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THE BACTERIOLOGY OF THE WOUNDS OF COMPOUND FRACTURES OF THE SKULL*

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ALTHOUGH it has been and is generally accepted that the degree of infection in compound fractures of the skull necessitates operative therapy within six hours and, more recently, that one of the sulfonamide compounds should be applied to the cleaned-up wound at the earliest possible moment, there has never been, to my knowledge, any attempt to measure this infection in terms of culturable bacteria. The fallacy of basing methods of treatment on tradition instead of on demonstrated facts has been abundantly emphasized in similar injuries to the long bones by the work of Orr in civilian life and by Trueta under conditions that exist in the field. This has caused, among other things, a new interest in and study of the degree and source of bacterial contamination of wounds and the methods by which contamination develops into infection locally and generally. As one of the direct results of this work, it must now be conceded that very few if any wounds of the extremities are originally and directly contaminated by pathogenic hemolytic streptococci, and that when such infection does develop in a wound it will be found to come from cross infection in the hospital or contamination by the attendant doctor or nurse, or because the patient himself is the carrier of the streptococci and infects his wound from his own upper respiratory passages. Miles[1] presents interesting data along this line. In a mixed group of 154 wounds, — 105 military (Dunkirk) and 49 air-raid injuries, — he found *Streptococcus haemolyticus* in only 25 per cent even though the swabs were not made until the patients had arrived in advance base hospitals in England. Nearly 9 per cent were "sterile." *Staphylococcus aureus* was grown from 53 per cent. In certain cases, by means of weekly cultures, he was able to identify at the start and to trace — to ward personnel, to patients in adjoining beds and to air-borne contamination from dressings, blankets and bed linen — streptococcal wound infections that later spread throughout a ward. Spooner[2] studied the bacterial contents of 31 air-raid wounds within forty-eight hours of their infliction, 13 plastered wounds between forty-eight hours and three weeks old and 29 plastered wounds more than five weeks old. In the air-raid wounds, there were 6 (19 per cent) from which no bacteria, 2 (6 per cent) from which "*Streptococcus pyogenes*" and 2 from which coagulase-positive (virulent) staphylococci were grown. There were 12 (40 per cent) including the above, from which pathogenic bacteria were obtained. Comparative figures from the two older series of cases were: no sterile wounds, 5 (38 per cent) and 20 (69 per cent) with streptococci, and 9 (69 per cent) and 19 (65 per cent) with pathogenic staphylococci. In a series of 355 industrial and other types of civil wounds in which cultures were taken within two hours of infliction, Hare and Willits[3] obtained similar results. Hemolytic streptococci of a nonpathogenic group were cultured from 2 cases (0.6 per cent), but no cases were noted from which pathogenic streptococci were isolated. No growth was obtained from 11.2 per cent. In considering staphylococcal infections, the authors give figures based on only 259 wounds. Staphylococci were isolated from 108 of these, but only 41 were coagulase-positive. As the result of this and other studies, they reiterate their formerly expressed opinion, "The majority of haemolytic streptococcal infections of wounds are not due to the introduction of the organisms at the time of infliction but afterwards from some outside source. . . ." They also note that, so far as their figures go and with consideration for the work of others — notably Smith,[4] whom they quote — and although "much further work is obviously necessary before the matter can be considered as settled . . . , the evidence so far available is cer-

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tainly suggestive of an exogenous rather than an autogenous source for many of the [staphylococcal] infections."

It has been my clinical experience that infection of the wounds in compound fractures of the skull is minimal during the first forty-eight hours after the injury. I[5, 6] have therefore repeatedly advocated postponement, for any necessary period up to forty-eight hours, of such major operative procedures as débridement. The postponement should last until after the patient is well out of surgical shock and until he is in an institution where personnel and equipment, including means for multiple blood transfusions, are available. I have always insisted, however, that as a corollary to this the first dressing must be one that only requires an absolute minimal handling of the wound and the débridement, when carried out, must be 100 per cent complete; one must actually excise all contaminated tissue without at the same time either spreading the contamination farther or causing tissue necrosis. Under such conditions, I[7] have found that it has been possible, provided that those patients whose death, disability or difficulty with wound healing was directly traceable to technical errors arising out of failure to meet these requirements were eliminated, to treat 218 cases of compound fracture of the skull of all kinds with a corrected operative mortality of 9 per cent and a rate of postoperative sepsis of 8 per cent (Table 1). This series includes bullet and perforating wounds, fractures into the various air sinuses, cerebrospinal-fluid rhinorrhea, multiple injuries, associated meningeal hemorrhages and all degrees of brain injury.

Such a concept of bacterial contamination and treatment has been disputed on two main grounds. The first is that the method was not in accord with what was and is often still considered to be the proper therapy of compound fractures of the long bones. The bacteriologic investigation noted above and a host of similar studies not included here answer this objection. Moreover, such work as that by Barnes[8] and Trueta[9] on wound infections emphasizes the relative unimportance of bacterial contamination and the relative value of immobilization of the wound during the first forty-eight hours, whether débrided or not, as a means of preventing this contamination from developing into an infection.

TABLE 1. *Classification of Cases of Compound Fracture of the Skull.*

Type of Fracture	All Cases			Cases without Operation			Cases with Operation					Cases with Operation Corrected for Technical Errors				
	No. of cases	No. of deaths	Death rate	No. of cases	No. of deaths	Death rate	No. of cases	No. of deaths	Death rate	Sepsis		No. of cases	No. of deaths	Death rate	Sepsis	
			%			%			%	*No.*	%			%	*No.*	%
Simple compound	153	40 (23*)	26	41	28 (23*)	67	112	12	11	31	28	91	4	4	6	7
Compound, involving the paranasal sinuses and without rhinorrhea	29	11 (0)	38	2	0 (0)	0	27	11	28	6	27	21	6	28	2	10
Compound, involving the paranasal sinuses and with rhinorrhea	12	2 (0)	17	3	1 (0)	33	9	1	11	0	0	9	1	11	1	11
Bullet wound	16	7 (6)	44	9	6 (6)	67	7	1	14	1	14	6	1	17	1	17
Perforating wound	6	0 (0)	0	2	0 (0)	0	4	0	0	1	25	3	0	0	0	0
Avulsion of scalp, with multiple trephinations	2	0 (0)	0	2	0 (0)	0	0	0	0	0	0	0	0	0	0	0
Totals	218	60 (29)	28	59	35 (29)	59	159	25	16	39	25	130	12	9	10	8

*The figures in parentheses indicate the patients dying within twenty-four hours.

The other criticism has arisen from the fact that no actual study of the bacteriologic contents of the wounds of compound fractures of the skull has been reported and that my theory as applied to this particular problem, although possibly true, had no bacteriologic facts to support it. I believe that the data presented herewith will answer this criticism, particularly since they conform with sufficient accuracy to the more extensive data concerning compound fractures of the long bones, as noted above.

Seventy patients with various types of compound fractures of the skull have had swabs taken from all depths of their wounds as well as from their noses, throats and ears and from two subcortical abscesses. The swabs were then plated for bacteriologic study. In addition, specimens of cerebrospinal fluid and blood were cultured and examined bacteriologically. The patients were divided as follows. In 10, the fracture was compounded not only through the skull but also into one of the paranasal air sinuses — usually the frontal; 6 of these patients died, and all were operated on and drained. In 7 with cerebrospinal rhinorrhea, 2 died. All but one were operated on; 3 cases were drained, and 3 were not, the fistula being closed by way of a transfrontal-flap craniotomy in the latter. Of 7 patients with

bullet wounds, 2 died; 2 were not operated on, 2 others were drained, and 3 were not drained, because the wounds healed by first intention. The bullet was removed in all but the patients who were not operated on, one of whom died of circulatory failure before his general condition warranted operation. The other is alive and well a year after his injury, although the bullet remains lodged in the base of his skull between the jugular bulb and the internal carotid artery. The arteriovenous fistula caused by its presence there has been closed by a ligation of the common carotid artery in the neck. Two patients with perforating wounds were operated on and survived, neither wound being drained. One of these patients had a previously unrecognized olfactory-groove meningioma at the time of his injury. This was removed after a subcortical abscess, which developed as the result of the improper treatment of the stab wound, had been healed up. Finally, there were 44 uncomplicated compound fractures. Four patients died, all following operation. Three others were not operated on. Eight patients, including 3 who died, had sepsis following operation. In 5 of these 8, including 2 of the deaths, the death and postoperative sepsis were directly traceable to improper therapy: 2 patients were operated on after the forty-eight-hour limit had passed, 2 had inadequate débridement, and in 1, tissue necrosis developed because of stitches that were too tight.

TABLE 2. *Organisms Recovered from Wounds of Compound Skull Fractures.*

ORGANISM	SIMPLE COMPOUND FRACTURES			COMPOUND FRACTURES INVOLVING PARANASAL SINUSES WITHOUT RHINORRHEA			COMPOUND FRACTURES INVOLVING PARANASAL SINUSES WITH RHINORRHEA			BULLET WOUNDS			PERFORATING WOUNDS			ALL FRACTURES		
	RECOVERED CASES	FATAL CASES	TOTAL CASES	RECOVERED CASES	FATAL CASES	TOTAL CASES	RECOVERED CASES	FATAL CASES	TOTAL CASES	RECOVERED CASES	FATAL CASES	TOTAL CASES	RECOVERED CASES	FATAL CASES	TOTAL CASES	RECOVERED CASES	FATAL CASES	TOTAL CASES
Str. haemolyticus	1	2	3	0	0	0	0	0	0	0	0	0	0	0	0	1	2	3
Str. haemolyticus and *Staph. aureus*	2	1	3	0	1	1	1	0	1	0	0	0	0	0	0	3	2	5
Staph. aureus	21	0	21	0	1	1	2	0	2	2	2	4	1	0	1	26	3	29
Staph. albus	7	0	7	0	0	0	0	0	0	0	0	0	0	0	0	7	0	7
Meningococcus	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
No growth	9	0	9	1	0	1	1	0	1	0	0	0	0	0	0	11	0	11
Totals	40	3	43	1	3	4	4	0	4	2	2	4	1	0	1	48	8	56

The cultures were grouped as follows: 1 from the ear, 4 each from the nose and throat, 2 from subcortical abscesses, 11 from the blood, 38 from the cerebrospinal fluid, 4 from the exposed calvarium, 4 from the dura, 4 from the wounds in the brain and 44 from the wound in general, making 112 in all. Because of variables in time and other factors, only cultures that were made from the wounds repay study. Fifty six of these were made on 52 patients. Pathogenic bacteria were grown from 38, or 67 per cent, of these cultures. All the bacteriologic work in this series was done under the direction of Dr. Robert N. Nye, assistant pathologist, and Miss Marion E. Lamb, bacteriologist, of the Mallory Institute of Pathology, Boston City Hospital. In accordance with the custom of the Bacteriology Laboratory, streptococci were reported only when they were of the pathogenic type. *Staph. aureus*, when reported, was also considered pathogenic, but *Staph. albus*, even though reported, was considered nonpathogenic, as were *Aerobacter aerogenes*, diphtheroids, and "spreaders." Pneumococci and meningococci were both reported and considered to be pathogenic, of course. *Escherichia coli* was reported once. At autopsy, it was found that the patient had died of *Esch. coli* meningitis. No attempt was made to culture any anaerobes. Aerobic cultures (blood broth and blood-agar plates) were incubated seventy-two hours, and if no bacteria had grown by the end of that time, a report of "no growth" was made. It is not suggested, and I do not believe, that the wounds whose cultures showed "no growth" were sterile. I believe there can be no doubt that all the wounds contained bacteria. However, the contamination was so slight in many that the swab did not come in contact with any of the contaminants.

Of the 38 cultures of pathogenic bacteria, 29 (76 per cent) showed *Staph. aureus* only, 3 (8 per cent) *Str. haemolyticus* only, and 5 (13 per cent)

a mixture of both (Table 2). Meningococci were grown from only 1 culture. If these figures are broken down still further, particularly in relation to the time elapsing between the infliction and swabbing of the wound, certain other significant data are apparent. Thirty-one wounds were swabbed within twenty-four hours or less of the receipt of injury. Of this group, 17 (55 per cent) showed pathogenic bacteria. No pure cultures of hemolytic streptococci were grown, and only 2 of mixed hemolytic streptococci and *Staph. aureus*. The remaining 15 all showed pure *Staph. aureus*. Forty-four wounds were forty-eight hours old or less when cultured. Twenty-six (66 per cent) grew pathogenic bacteria. Of these, 1 (4 per cent) grew *Str. haemolyticus*, and 4 (15 per cent) a mixture of this organism and *Staph. aureus*. The remaining 21 showed pure *Staph. aureus*. Twelve wounds were cultured when they were over forty-eight hours old. Eleven, or 91 per cent, contained culturable pathogenic bacteria. Thus, the percentage of compound fractures of the skull that contained cultural pathogenic bacteria within the wounds rose from 55 in the first twenty-four hours through 66 in the first forty-eight hours to 91 after forty-eight hours had elapsed between the receipt of the wound and its swabbing for culture. The conclusion seems inescapable from these figures that the rate of contamination of such wounds is essentially stationary for forty-eight hours after their infliction, but that thereafter it rises rapidly to the neighborhood of 100 per cent.

There were 7 patients from whose wounds hemolytic streptococci were cultured eight times. Three of the cultures were pure, and the rest were mixed with *Staph. aureus* alone twice and with both that and *Staph. albus* three times. Three wounds were cultured at operation, and only 2 of these within twenty-four hours of the infliction of the wound. One of the latter patients had a very extensive compound fracture of the frontal bone, with practically complete destruction of the posterior wall of one frontal sinus and a wide-open communication between the nose and the meningeal spaces. The other had a simple compound fracture. The wound had been treated only by covering with a sterile gauze pad. This is the sole case in which the streptococcus might have been introduced at the time the wound was made. The patient was struck about the head and face by an assailant who used an iron bar. The skull was fractured in the right parietal and left temporal regions. Another culture, made from this wound fourteen days postoperatively, was also positive for hemolytic streptococci. This patient survived. In the third patient and the 4 succeeding ones, all the wounds were cultured forty-eight or more hours after infliction. The third patient was another whose fracture was compounded not only externally but also into a frontal sinus. He was not brought to the hospital until twenty-four hours after he had been injured. The wound was cultured forty-eight and débrided fifty-five hours after infliction. Meningitis was already present when the débridement was performed. This patient died. The other cultures were made two, two, ten and twelve days after infliction, or one, one, nine and eight days after operation. In view of the time that elapsed between the injury and the postoperative culture, there was ample opportunity for implantation of streptococci into these last five wounds after their infliction and before they had been cultured or débrided. Of these 5 patients, 4 died, 2, partly at least, because débridement was postponed for fifty-five hours in one case and was not done at all in the other, with the result that meningitis supervened in the first and a cortical abscess in the second. Death in the other 2 cases was from meningitis, despite the fact that all technical requirements had been met. The fifth patient survived in spite of a complicating meningitis. The technic used was satisfactory. No throat or nose cultures were made from any of these 7 patients.

In 1 patient, meningococci were cultured from the wound seven days after its infliction and one day after operation. The fracture in this case was compounded through the frontal bone and also into one frontal sinus. At operation, six days after the injury, the wound was irrigated. The patient died of meningitis and a frontal-lobe abscess. The meningococcus certainly originated in the nose and was spread by the irrigation.

Pneumococci were cultured from 3 patients. All had fractures compounded into the nose, 1 by way of one frontal sinus and the other 2 by way of the cribriform plate, both the latter being accompanied by cerebrospinal rhinorrhea. The first patient was not operated on, and the pneumococcus was cultured from the cerebrospinal fluid ten days after the injury and in the presence of a meningitis. The second case was similar in that no operation was performed, but the bacterium was cultured from the cerebrospinal fluid four days after the injury. A positive blood culture was obtained in this case at the same time. Sulfapyridine had been given by mouth from the start. Both these patients died. In the third patient, the cerebrospinal-fluid fistula was closed within twenty-four hours of the injury by way of a transfrontal bone-flap operation. Just previous to this, a culture of the nose had proved positive for pneumococci. The wound healed by first intention, and the patient recovered. None of the sulfonamide group of drugs were used in this case.

There were 3 deaths among the patients from whose wounds *Staph. aureus* was grown. All were directly traceable to errors in technic. In 1 case, meningitis followed forcible removal of a Mosher cone-shaped copper-wire drain about three weeks after operation for a compound fracture of the frontal bone that involved one frontal sinus; another patient died of *Esch. coli* meningitis following a débridement that was not done for sixty hours after the accident; this patient was given sulfapyridine by mouth. In the third patient, who had a bullet wound, the débridement had to be postponed for forty-eight hours because of the patient's general condition. Sulfapyridine was given by mouth and sulfanilamide put in the wound from the first, and the wound was closed at operation. The patient died from meningitis. Three other patients recovered but had sepsis in their operative wounds. In 2 cases, no cause for the sepsis could be found in the technic, but in the third,—a perforating wound, in which débridement was not done,—a cortical abscess followed.

There were 20 wounds in which the cultures were reported as showing either no growth or *Staph. albus*. Three of these patients died—all in the "no growth" group. Two wounds were compound fractures of the frontal bone, with extension into one frontal sinus. One patient, who was not operated on, died of pneumococcal meningitis, and the other died four days after operation of a meningitis whose cause was not identified. The third patient, with a bullet wound, died of circulatory failure before he could be operated on. Four other patients, who recovered, had sepsis or wounds that failed to heal by first intention. The sepsis was traceable to technical errors in every case. One, with a compound fracture of the frontal bone and involvement of the frontal sinuses, who was not operated on until six days after injury, developed a secondary frontal subcortical abscess, which later had to be drained. Another, with an uncomplicated compound fracture, was not brought to the hospital until sixty hours after injury, and although the wound was partially débrided two hours later, it was considered better judgment to pack the wound and allow it to heal by second intention rather than to close it at once. The third patient—a similar case to the last—was not brought to the hospital for five days. No operation was performed, the wound being merely packed wide open. The last case was also an uncomplicated compound fracture in which it was decided to substitute chemotherapy for surgery—sulfapyridine was administered by mouth and sulfanilamide put in the wound. The wound granulated but refused to heal completely until, at the end of two weeks, exploration disclosed a "rock" of sulfanilamide. This was removed, after which the wound healed promptly. There were no deaths or sepsis among the 9 patients from whose wounds cultures yielded *Staph. albus* only.

Discussion

It appears from this material that the degree of culturable contamination of the wounds of compound fractures of the skull varies from 55 to 66 per cent during the first forty-eight hours after infliction, *provided* the wound is not "massaged" during that period. The rise during the second twenty-four-hour period is statistically minimal, and it probably makes little difference at what time during this forty-eight-hour period the débridement is done, provided it is 100 per cent complete. If these requirements are fulfilled, and particularly if inhibition of further growth of bacteria is aided by proper chemotherapy, postoperative infection of such wounds should be reduced to something closely approximating that seen after uncontaminated surgical wounds anywhere in the body. The contention that pathogenic hemolytic streptococci are not deposited in the wound at the time of its infliction, as advanced by Hare and Willits[3] and others in compound fractures of the long bones, must be considered to hold true also in compound fractures of the skull with one exception. This refers to fractures that involve the paranasal sinuses and applies not only to hemolytic streptococci but also to meningococci and pneumococci. Except for multiple small perforating wounds, with many fragments of foreign bodies scattered throughout the substance of the brain, I see no reason so far as this experience goes, to differentiate either bacteriologically or therapeutically bullet wounds from other types of compound fractures of the skull. This is in general accord with recent experience with compound fractures of the long bones as cited by Trueta[9] and others. Moreover, this evidence supports the contention of Trueta and of Barnes[8] that immobilization of the wound is the critical factor if, for immobilization, one means a "minimum of handling at the first dressing of the wound" and until the débridement is done. It must be evident that this dictum is much more important and more in accord with the established facts than any shibboleth that is based on tradition. There is no "golden six-hour interval" in which surgery of compound fractures of any bone whether long or flat *must* be practiced. If the bacteria contaminating a wound are "stirred with a spoon" or the tissues contaminated by these bacteria are "massaged," a thirty-minute interval between infliction and débridement is too long to wait before one deals with the infection that has been conjured up

out of what was only a contamination. If the contamination is recognized for what it actually is and treated with the respect it merits, infection can be prevented from developing by a proper débridement carried out at any time within the first forty-eight hours after infliction of the wound, provided the patient is safely out of surgical shock and in a properly equipped and staffed hospital.

Summary

A report of 112 cultures made from 70 patients with varying types of compound fractures of the skull is presented.

Fifty-six wound cultures were taken in 52 cases. The incidence of infection in the wounds of these compound fractures of the skull was 55 per cent during the first twenty-four hours, 66 per cent during the first forty-eight hours, and 91 per cent after forty-eight hours had elapsed between infliction and swabbing of the wound.

Pathogenic hemolytic streptococci were grown from the wounds of only 7 patients, in only 1 of whom there was evidence that the contamination could reasonably have taken place at the time of infliction of the wound.

These results conform in general to those obtained from the study of certain series of wounds in other parts of the body received in military action, in the course of air-raids and in civil life.

They emphasize the value of immobility of the wound or its equivalent in all compound fractures as a means of preventing contamination from becoming infection, and the lack of significance of the local growth of bacteria as the cause of this change.

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PLASMA PROTHROMBIN AND LIVER FUNCTION DURING SULFONAMIDE THERAPY*

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THERE have been described two types of injury to the liver resulting from therapy with the sulfonamides. Jaundice and signs of diminished hepatic function may accompany the acute hemolytic crises that occasionally occur following the administration of these drugs. Secondly, a primary hepatitis may result as a direct toxic effect of the chosen drug on the liver cells.

The acute hemolytic crisis with a rapidly progressive anemia may come on at any time following the onset of drug administration, and usually occurs within three to five days. Wood[1] found the anemia to occur only in febrile patients. The hemoglobin may fall rapidly to 20 to 30 per cent of normal, and this is accompanied by a rise in temperature, polymorphonuclear leukocytosis, reticulocytosis and an increase in immature cells, with evidence of hyperactivity of the hematopoietic system. Hemoglobinuria may occur.[2] In some cases this is accompanied by jaundice, with evidence of hepatitis and diminished hepatic function. The hepatitis may be mild and clear up rapidly after the drug is stopped. The severe cases may go on to acute yellow atrophy and death. The presence of jaundice in hemolytic anemia has been ascribed mainly to the hemolytic process, but direct liver damage may coexist with it.[3]

There have been a number of reports indicating an apparent primary acute toxic hepatitis with jaundice and decreased liver function during or subsequent to sulfonamide therapy, with several deaths. The importance and the serious nature of this complication are indicated by the fact that nearly all the fatalities resulting from the sulfonamide drugs have been due to agranulocytosis, toxic hepatitis or hemolytic anemia. Hageman and Blake[4] noted 1 case of toxic hepatitis with recovery in a group of 114 patients receiving sulfanilamide, and Bannick, Brown and Foster[5] reported 2 deaths. Cline[6] reported autopsy findings of acute yellow atrophy following the administration of 45 gm. of sulfanilamide. Saphirstein[7] had a severe but nonfatal case of toxic hepatitis following the use of this drug, with an associated der-

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matitis which was exfoliative in character. This has been seen to accompany the hepatitis in several other cases reported in the literature. Garvin[8] reported 5 cases with 1 death, and Berger and Applebaum[9] reported autopsy findings of subacute liver atrophy following sulfanilamide. Other cases of toxic hepatitis have been reported by Ottenberg,[10] Fitzgibbon and Silver,[11] Gertler[12] and Russell.[13] A fatal case reported by Tragerman and Goto[14] showed degeneration of the liver cells. Greene and Hotz[15] mention 4 cases of hepatitis with 2 deaths, and found an increase in the sulfanilamide level in the liver in a patient with hepatitis. Spring and Bernstein[16] reported 2 cases in which there was a coexistence of toxic hepatitis with acute hemolytic anemia and renal damage following sulfanilamide.

Long, Haviland, Edwards and Bliss[17] found that the incidence of toxic hepatitis, as indicated by jaundice without anemia and a definite impairment of liver function, occurred in 0.6 per cent of 1000 hospitalized adults receiving sulfanilamide therapy. Many other authors have noted mild attacks of jaundice without anemia, which usually subsided rapidly on discontinuation of the drug. The incidence of these occasional complications is not inappreciable. Jaundice appears to be commoner after sulfanilamide than after other drugs of the sulfonamide series.

Hepatitis may occur early or late in the course of therapy, and may even first be observed up to six days after the drug has been discontinued. In most of the cases reported the dosage has not been particularly large, and in almost all cases was below 50 gm. The hepatitis may take the form of toxic necrosis or of acute yellow atrophy. Jaundice, hepatomegaly, splenomegaly and ascites may occur. There is usually an immediate direct van den Bergh reaction, increased urobilinogen in the urine and decreased hepatic function. Often a high temperature and leukocytosis occur with the hepatitis, and the patient is acutely ill. In mild cases the prognosis is usually good if the drug is immediately stopped, fluids forced and supportive treatment instituted. However, the hepatitis may progress in spite of the discontinuance of the drug, as illustrated by 2 of the cases presented by Garvin.[8]

Materials and Methods

All patients studied in the present series were on the surgical wards of the Massachusetts General Hospital in the spring and summer of 1941, and had infections of the average type found on a general surgical service. These included cellulitis, abscess, carbuncle, thrombophlebitis, bacteriemia, urinary infection, osteomyelitis, acute pulmonary and pelvic infections, and ulcer. About half the patients were acutely ill with marked febrile reactions; the remainder had more chronic, less virulent infections. The drugs used were sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine. The dosages varied from as little as 3 to 8 or 9 gm. per day.

The liver-function tests selected for study were the bromsulfalein excretion, the van den Bergh reaction and the prothrombin time. The Quick[18] technic was used for this latter test.

It has been pointed out that reduction in the plasma-prothrombin level may be an early and very sensitive indication of decline in hepatic reserve.[19] Wilson[20] found a close correlation between the level of plasma prothrombin and the hippuric acid liver-function test. In patients with liver damage these two were more sensitive measures of hepatic damage than any other liver-function test. However, in any toxic reaction to the liver it is possible that the different functions of this organ may be affected to a varying extent. One function may show severe incompetence, while another is completely unaffected.

The tests in our series were carried out before the drug was begun, and at intervals until several days after the drug was discontinued.

Data

Sixty-eight patients in all were studied, and of these 14, or 21 per cent, showed an appreciable increase in prothrombin time during the course of chemotherapy. Only a few of the latter showed changes in bromsulfalein excretion or in the van den Bergh reaction. No patient showed changes in these latter two without, in addition, showing a fall in the level of plasma prothrombin.

The cases with significant increases in prothrombin time are abstracted below.

Case Reports

Case 1. J. P., a 39-year-old Finnish housewife with known biliary cirrhosis of 2 years' duration, was admitted for study of generalized xanthomatosis of 2 months' duration. She had been under treatment with parenteral and oral vitamin K for 9 months because of a prolonged prothrombin time. A biopsy of one of the xanthomatous nodules was performed, and 6 days later the patient developed a cellulitis and erysipelas, with redness, pain, lymphadenitis, a temperature of 103.4°F. and a white-cell count of 19,100. Cultures of the leg showed a virulent beta hemolytic streptococcus (Group A, Lancefield) and coagulase-positive *Staphylococcus aureus*. In view of the liver damage it was thought that chemotherapy was inadvisable, but the patient developed a chill and extension of the clinical signs of infection. The prothrombin time was 21 seconds (21 seconds*) and the van den Bergh reaction was 5.4 mg. per 100 cc. The patient was given 6 gm. of sulfanilamide initially, then 1 gm. every 4 hours. She was also given 32,000 units of scarlet-fever antitoxin and an immune transfusion because of the absence of opsonic antibodies from the blood. The infection improved rapidly but on the seventh day of chemotherapy

*All figures in parentheses indicate the normal prothrombin time.

the prothrombin time was 85 seconds (23 seconds) and the van den Bergh reaction was 6 mg. per 100 cc. The chemotherapy was stopped and intravenous vitamin K was given. Within 24 hours the prothrombin time was normal.

CASE 2. L. T., a 64-year-old Negress, had a radical mastectomy for adenocarcinoma. Postoperatively she developed a staphlyococcal infection of the wound, which was drained. She appeared to be doing well but suddenly developed erysipelas, with a temperature of 105°F. and redness and an erysipeloid reaction about the wound. The prothrombin time and van den Bergh and bromsulfalein tests were all normal. The patient was given 4 gm. of sulfapyridine initially, then 1 gm. every 4 hours. She also received 32,000 units of scarlet-fever antitoxin and an immune transfusion. A blood culture showed two colonies per cubic centimeter of beta hemolytic streptococcus (Group A). The temperature returned to normal in 48 hours. On the 3rd day of chemotherapy the prothrombin time was 29 seconds (23 seconds), the van den Bergh reaction was negative, and the bromsulfalein test showed a 5 per cent retention. On the 7th day of chemotherapy the prothrombin time was 32 seconds (23 seconds), the van den Bergh reaction was negative, and the bromsulfalein test showed a 12 per cent retention. The drug was discontinued, and on the 10th day all the tests were normal.

CASE 3. M. D., a 38-year-old housewife, was admitted for repair of a ureterovaginal fistula. At operation the ureter was implanted into the dome of the bladder and sulfanilamide powder was placed in the wound. On the 3rd postoperative day the patient developed pyelitis. A blood culture taken at this time yielded *Escherichia coli*. The prothrombin, van den Bergh and bromsulfalein determinations were all normal. Sulfapyridine was given in a dosage sufficient to maintain a blood level of between 10 and 12 mg. per 100 cc. On the 4th day of chemotherapy the prothrombin time was 38 seconds (23 seconds), the van den Bergh reaction was negative, and the bromsulfalein retention was 8 per cent. On the 5th day o chemotherapy the prothrombin time was 38 seconds (23 seconds). The chemotherapy was omitted and Hykinnone was given parenterally. Twenty-four hours later the prothrombin time was normal. Four days later the bromsulfalein retention and the van den Bergh reaction were also normal.

CASE 4. J. C., a 43-year-old Negro, entered the hospital with bilateral chronic pulmonary suppuration, apparently not tuberculosis, and a secondary pneumonia. The blood Hinton test was positive, and there was evidence of cardiovascular syphilis with an aneurysm. The control prothrombin time was 25 seconds (22 seconds) and the van den Bergh and bromsulfalein determinations were negative. The patient was started on 4 to 6 gm. of sulfathiazole daily. On the 5th and 9th days of therapy the prothrombin time was 30 seconds (22 seconds). At this time the drug was changed to sulfapyridine, 4 gm. daily. After 5 days the prothrombin time was 30 seconds (23 seconds), the van den Bergh determination showed a trace, and the bromsulfalein retention was 5 per cent. Chemotherapy was discontinued because of no results. Three days later the prothrombin time was 24 seconds (22 seconds).

CASE 5. L. H., a 37-year-old chauffeur, entered with a 5-day history of abdominal pain, anorexia, nausea and vomiting. Examination revealed a mass in the right lower quadrant of the abdomen, and a diagnosis of a perforated appendix with abscess was made. The appendiceal abscess was drained, and an appendectomy was done. Sulfapyridine was placed in the wound and was given intravenously in a dosage to maintain a blood level between 8 and 9 mg. per 100 cc. The control prothrombin time was 25 seconds (23 seconds), a bromsulfalein test showed 7.5 per cent retention, and the van den Bergh reaction was 2.4 mg. per 100 cc. On the 2nd day of chemotherapy the prothrombin time was 32 seconds (23 seconds); 3.2 mg. of Hykinnone was given. On the 4th day the prothrombin time was 37 seconds (23 seconds), the bromsulfalein retention was 5 per cent, and the van den Bergh reaction was 2.6 mg. per 100 cc. Chemotherapy was discontinued at this time owing to drug fever. The prothrombin time gradually returned to normal, and on the 11th day after the drug was stopped it was 26 seconds (23 seconds) and the van den Bergh determination was 1.7 mg. per 100 cc.

CASE 6. R. H., an 8-year-old Negro, blind since birth, was admitted because of a furuncle of the leg and septicemia. A blood culture yielded a coagulase-positive *Staph. aureus*. The control prothrombin and van den Bergh determinations were normal. The patient was started on sulfathiazole, with a dosage of 6 to 9 gm. daily. He developed a subperiosteal abscess of the tibia, which was drained with ligation of the femoral vein. He then showed evidence of pulmonary miliary tuberculosis. The prothrombin time gradually increased, and on the 15th day of chemotherapy it was 38 seconds (22 seconds) and the van den Bergh reaction was 2.4 mg. per 100 cc. Hykinnone was given at this time, and the prothrombin time returned to normal within 24 hours and remained so until death 4 days later from acute tuberculosis. Shortly before death the van den Bergh was 2.8 mg. per 100 cc. and the bromsulfalein test showed 20 per cent retention.

CASE 7. L. W., a 53-year-old woman, was admitted with a septic prepatellar bursitis, which had developed 2 weeks after a fall. A culture yielded an attenuated microaerophilic beta hemolytic streptococcus (Group A) and a coagulase-positive staphylococcus. The control prothrombin time was 21 seconds (23 seconds), the van den Bergh reaction showed a trace, and the bromsulfalein test was negative. The knee was drained, and the patient was started on sulfanilamide, with a dosage of 4 gm. initially and 6 gm. daily for 8 days, blood levels between 9 and 11 mg. being obtained per 100 cc. On the 6th day of chemotherapy the prothrombin time was 34 seconds (22 seconds), and on the 8th day it was 37 seconds (22 seconds). The van den Bergh and bromsulfalein determinations remained normal throughout. The drug was discontinued because the patient developed a rash, the urine was loaded with sulfanilamide crystals and young red and white cells were present in the blood. Two days later the prothrombin time was 28 seconds (22 seconds); 3 days later it was 24 seconds (22 seconds).

CASE 8. D. W., a 9-year-old girl, was admitted with a diagnosis of osteomyelitis of the knee and staphylococcal bacteriemia. She had received chemotherapy prior to admission. The control prothrombin time was 31 seconds (22 seconds), and the van den Bergh reaction was negative. The patient was started on large doses of sulfadiazine, 9 to 11 gm. per day, and the usual supportive treatment. After 5 days the prothrombin time was nor-

mal and showed no further change, in spite of larg amounts of sulfadiazine.

Case 9. W. W., a 23-year-old man, was admitted with a diagnosis of acute gonococcal urethritis and a possible arthritis. The control prothrombin time, van den Bergh, and bromsulfalein reactions were all normal. He was started on a dosage of 6 gm. of sulfathiazole daily. After 21 days of chemotherapy the prothrombin time was 31 seconds (22 seconds). The drug was omitted, and the prothrombin time returned to normal within 48 hours.

Case 10. L. F., a 46-year-old woman, was admitted with a diagnosis of pelvic inflammatory disease and peritonitis. The control prothrombin, van den Bergh and bromsulfalein tests were all normal. Treatment with sulfapyridine was begun, and later the patient was shifted to sulfathiazole. On the 12th day of chemotherapy the prothrombin time was 31 seconds (22 seconds); on the 14th day it was 34 seconds (22 seconds). The patient became acutely ill, developed thrombophlebitis of the pelvic veins, and was heparinized. Two days after heparin was discontinued, the prothrombin time was 70 seconds (22 seconds) and the van den Bergh reaction was 2.4 mg. per 100 cc. Two days later the prothrombin time was 51 seconds (22 seconds), the van den Bergh reaction was 3 mg. per 100 cc., and the bromsulfalein test showed 20 per cent retention. The following day the prothrombin time was 32 seconds (22 seconds), the van den Bergh reaction was 2.2 mg. per 100 cc., and the bromsulfalein test showed 20 per cent retention. At this time treatment was begun with vitamin K, and 4 days later the prothrombin time was normal, but the bromsulfalein reaction did not return to normal until 1 week later, at which time there was a trace in the van den Bergh reaction.

Case 11. E. L., a 23-year-old man, was admitted for a pneumonectomy for bronchiectasis, at which time sulfanilamide powder was placed in the pleural cavity. The control prothrombin, van den Bergh and bromsulfalein determinations were all normal. The patient was started on 6 gm. of sulfapyridine daily. On the 5th day of chemotherapy the prothrombin time was 30 seconds (22 seconds); on the 8th day it was 35 seconds (22 seconds). On the 10th day microscopic hematuria developed and the drug was stopped. Six days later the prothrombin time was 29 seconds (22 seconds). Three days later it returned to normal. The van den Bergh and bromsulfalein determinations remained unchanged throughout.

Case 12. J. C., a 36-year-old man, was admitted for resection of a chondrosarcoma of the sternum, which was complicated postoperatively by pneumonia. The prothrombin time was 25 seconds (23 seconds), and the van den Bergh and bromsulfalein determinations were normal. Sulfapyridine therapy was begun. On the 4th day of chemotherapy the prothrombin time was 33 seconds (22 seconds), the van den Bergh reaction was 1.6 mg. per 100 cc., and the bromsulfalein test showed 5 per cent retention. Chemotherapy was stopped at this time. The patient died the following day.

Case 13. T. P., a 39-year-old policeman, entered with a diagnosis of cellulitis of the scalp. The prothrombin time was 24 seconds (22 seconds), the van den Bergh reaction showed a trace, and the bromsulfalein retention was normal. Three grams of sulfathiazole was given initially. A culture of the wound yielded an attenuated beta hemolytic streptococcus (Group A) and a coagulase-positive staphylococcus. The drug was changed to 8 gm. of sulfanilamide daily, which maintained a blood level between 9 and 12 mg. per 100 cc. On the 2nd day of chemotherapy the prothrombin time was 28 seconds (22 seconds), and on the 5th day it was 30 seconds (22 seconds). At this time the dosage was halved. In 2 days the prothrombin time was 26 seconds (22 seconds), the van den Bergh determination showed a trace, and the bromsulfalein test showed 5 per cent retention. Shortly after this the patient developed bilateral deep phlebitis with a positive Homans's sign, which was partially relieved by a paravertebral novocain block. Chemotherapy was omitted, and 3 days later the temperature went to 104°F. and the patient developed an acute hemolytic anemia, with a red-cell-count drop to 1,700,000. The prothrombin time was 32 seconds (22 seconds). Three transfusions were given, and the hemolytic crisis lasted only about 24 hours. The prothrombin time returned to normal in 4 days.

Case 14. J. R., a 28-year-old man, was admitted with a carbuncle of the neck and a *Staph. aureus* bacteriemia. The temperature was 106°F. on admission but the prothrombin time and van den Bergh reaction were normal. The patient was started on sulfadiazine, 9 to 12 gm. daily, to maintain a blood level between 15 and 20 mg. per 100 cc. The day following admission he developed a thrombophlebitis of the side of the neck and pleuritic chest pain. Accordingly, ligation of the external and internal jugular and middle thyroid veins was carried out and the carbuncle was excised. On the 5th day of chemotherapy the prothrombin time was 30 seconds (22 seconds). The patient recovered.

Discussion

Watson and Spink[3] did not observe jaundice in any adult receiving less than 3 gm. of sulfanilamide per day, and no increase of urinary urobilinogen in these cases. We found no change in prothrombin level in any case receiving 4 gm. or less of sulfonamide per day. When daily doses of 4 to 8 gm. are given, it is obvious that in a considerable proportion of patients there is a definite decrease in the plasma-prothrombin level. Most of these patients were acutely ill and highly toxic, and many had high temperatures. However, fever alone was not accompanied by a decrease in the prothrombin level. Many of our patients were taking little food by mouth and were being sustained with parenteral fluids. Because of the short period of time involved, it is unlikely that inadequate dietary intake was a factor in the decrease of plasma prothrombin. Whether prothrombin deficiency can occur in man solely on the basis of insufficient food intake is still doubtful.[19]

The type of infection seemed to make no difference in these cases. It is well known that toxic hepatitis, with jaundice and reduction in plasma prothrombin, may occur in severe infections or in chronic sepsis.[19, 21] The cause is unknown, although this complication appears to be commoner in cases of peritoneal sepsis. Hence, in these cases both the infection and the chemotherapy exert a hepatotoxic effect. That the infection may play a

considerable accessory role in the depression of liver function is shown by the fact that patients on chemotherapy who had severe infections showed changes in prothrombin levels much more frequently than did those with minor infections.

In the cases reported in the literature only 1 has had serologic evidence of syphilis, and only 1 of ours was similarly affected. Hence this does not appear to be a factor.

In our cases, depression of the plasma-prothrombin level occurred with all four of the drugs used — sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine. We do not have enough cases to warrant any statistical analysis concerning the relative frequency with which this occurs with the different drugs. However, sulfadiazine was used in only 1 of our cases with an increased prothrombin time, and this was quite mild. In another case, there was a depression of prothrombin level with sulfathiazole, which cleared up on discontinuance of the drug and did not recur later on when sulfadiazine was given.

In most cases, depression in prothrombin level did not occur until the drug had been used for four or five days. In 1 case, however, it occurred forty-eight hours after the drug was begun. In most cases the prothrombin levels returned to normal within a few days after the drug was discontinued. In 1 case, however, a week was necessary.

There is probably an increased incidence of hepatitis in patients with previous liver damage or alcoholism. In 1 of our patients, who had a severely damaged liver, there was a sudden and marked fall in prothrombin level when chemotherapy was begun. However, in most cases, chemotherapy can be continued for some time with little or no effect on the liver. A sulfonamide drug has been given to patients with cirrhosis or jaundice without untoward results.[22]

None of our patients developed jaundice and clinical evidence of toxic hepatitis. This may have been due to the fact that the drug was discontinued or used with great caution in those patients who showed changes in the plasma-prothrombin level. In all cases this level returned to normal after stopping of the drug, and there was no evidence of any permanent impairment of liver function. In all cases in which parenteral vitamin K was given, the prothrombin time was normal within twenty-four hours, indicating that the liver was able to respond.

Usually the first sign noted clinically that warns the physician of the occurrence of toxic hepatitis is the appearance of jaundice. By this time it may be too late to prevent a fatality or a major illness superimposed on the patient's infection, even if the drug is promptly stopped. Weir[23] has pointed out that hepatitis, even to the extent of fatal acute yellow atrophy, can occur without jaundice. Slowly progressive changes in the liver may follow a bout of acute hepatitis in spite of apparent complete recovery, and advanced cirrhosis may follow an old acute hepatitis that never produced any clinical symptoms.[24] Since changes in the prothrombin level appear to be an early indication of impending liver damage, the test is of great help in avoiding this major complication.

Although the cause of the hepatitis following sulfonamide therapy is unknown, two possibilities have been considered. It may be another example of drug hypersensitivity, which occurs in an occasional patient owing to idiosyncrasy, or these drugs may regularly produce evidence of hepatic dysfunction. In the case cited by Fitzgibbon and Silver[11] and in several others in the literature, there was an interval of several weeks between courses of the drug, and this suggests the former explanation. However, since so many cases show some evidence of liver damage, it is clear that these drugs are inherent liver poisons. A severe hepatitis is probably an accentuation of a usual toxic effect rather than a true drug idiosyncrasy. However, both these factors may play a role in certain cases.

Probably all factors that tend to depress liver function will exaggerate the effects of the sulfonamides in reducing liver function. Hence all possible measures to maintain liver reserve should be taken in patients receiving chemotherapy. It has recently been shown that a high-protein (casein) diet protects rats being given large amounts of sulfanilamide daily.[25]

Conclusions

Liver function, as measured by prothrombin, van den Bergh and bromsulfalein tests, was measured in 68 patients receiving sulfonamide therapy for acute infections. Fourteen patients, or 21 per cent, showed a significant decrease in the prothrombin level during chemotherapy. The severity of the infection seemed to be more significant as the cause of prothrombin depression than did the type of sulfonamide used. It is recognized that decreased prothrombin time may be the consequence of factors other than impaired liver function. Inasmuch as serious infection and sulfonamides are both prejudicial to the welfare of the liver, it seems wise to recommend some test of liver function as a routine procedure in this group of patients.

A decrease in plasma prothrombin is found early in impending liver failure. The Quick[18] method of plasma-prothrombin determination is simply and easily performed and is relatively inexpensive. It is suggested that such prothrombin determinations be done every three days in seriously ill pa-

tients receiving sulfonamide therapy. In this way it should be possible to recognize patients in whom serious hepatitis is apt to develop before the symptoms have become clinically alarming.

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SIMULTANEOUS HYPERFUNCTION OF THE THYROID AND PARATHYROID GLANDS*

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THE concurrence of hyperthyroidism and hyperparathyroidism is a clinical rarity; a patient with such a syndrome forms the basis of this report. She presented a confusing symptomatology, so that in retrospect it seems worth while to indicate the clues that could have led to a preoperative diagnosis. Although such a combination is unusual, this case is by no means an isolated example.

Case Report

M. W., a 51-year-old, married housewife, was admitted to the Medical Service of the Peter Bent Brigham Hospital on November 4, 1941. She complained of weakness, abdominal distress and vomiting of 8 months' duration. The past history was of interest in that 10 years previously her physician had noted that her thyroid gland was enlarged. Four years previously she passed what was thought to be a renal calculus. She had no other urinary symptoms. One year prior to admission there occurred a 3-week episode of vomiting and abdominal pain, diagnosed as gallbladder disease. From 16 months until 2 months before admission the patient took 1 tablet of thyroid each day. The basal metabolic rate was not determined. The menstrual periods had been irregular and infrequent during the preceding 2 years.

In March, 1941, the patient began to lose weight. This proceeded steadily until she had lost 40 pounds. During the summer the heat oppressed her much more than usual. At the same time she developed abdominal soreness and nausea. Coincidentally there were generalized weakness and exertional dyspnea, which became so marked that she was forced to remain in bed for 6 weeks prior to admission. During the latter period she vomited eight to ten times a day. In addition she was irritable and noticed that the swelling in the neck was larger. One month before entry, daily iodine therapy was instituted but resulted in no improvement.

Physical examination on admission showed a thin woman with evidence of considerable weight loss. The weight was 108 pounds. She was alert and hyperactive. There were generalized muscular weakness and atrophy, with a fine tremor of the hands. The skin of the body was warm and dry, but the hands were cool. The eyes were staring and there was lid lag. There was a fine tremor of the tongue. The thyroid gland was moderately and symmetrically enlarged, with a soft bruit. The heart was normal in size and rhythm, but the rate was 120 to 140 even after several hours of bed rest. The blood pressure was 145/65. The tip of the spleen could be felt. The abdominal aorta and iliac vessels were easily palpable and sensitive, and this maneuver elicited considerable nausea. The deep tendon reflexes were very active.

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The hemoglobin was 10.1 gm., and the blood smear was normal except for moderate variation in the size and shape of the red cells. Urinalysis was negative. The serum cholesterol was 181 mg. per 100 cc. The gastric contents contained free acid after histamine. The basal metabolic rates in a series of determinations were +36, +29, +23, +25 and +31 per cent. The decholin circulation time was 12 seconds. The heart and lungs were negative to x-ray examination, although the trachea was displaced to the left. The bony thorax was normal. A gastrointestinal series demonstrated no abnormalities. Prostigmine injection produced no change in muscular activity.

During the patient's stay on the Medical Service her temperature fluctuated each day, rising as high as 101°F. by rectum. The heart rate was usually between 120 and 150, even during sleep. She was hyperactive and retched frequently. She had been taking iodine during the month prior to admission, and this drug was continued. Myasthenia remained a prominent aspect of the symptomatology. There was no clinical improvement, and on November 17 the patient was transferred to the Surgical Service for thyroidectomy.

The following day operation was performed under novocain anesthesia. A rather large, vascular, hyperplastic thyroid gland was found, and a radical subtotal thyroidectomy was performed. In addition, there was a yellowish tumor at the lower pole of the left lobe, which had the gross appearance of a parathyroid gland. Venous blood was taken for chemical determinations, and the tumor was removed.

Significant blood studies were as follows:

Time	Calcium	Phosphorus	Phosphatase
	mg./100 cc.	*mg./100 cc.*	*Bod. units/100 cc.*
At operation..	17.2	2.5	3.2
Postoperative day:			
2nd	16.4	3.1	
4th	11.4	1.0	
6th	11.4		
9th		2.4	
14th	7.6	2.2	
Normal	9–11	2.5–4.5	2–4

It is evident that during and immediately after operation this patient's serum calcium was considerably elevated whereas the phosphorus was decreased — findings that are typical of hyperparathyroidism. The normal phosphatase level was consistent with the paucity of bone changes.

The postoperative course was uneventful except for the development of mild tetany on the 7th day, controlled with calcium gluconate intravenously. Other x-ray studies at this time demonstrated a nonfunctioning gall bladder. Films of the long bones showed the bone detail and calcium content to be normal except for slight osteoporosis of the femurs. Skull films revealed a normal sella, with a mild degree of osteoporosis of the vault. Intravenous urograms were normal. Moderate hypochromic anemia persisted. Three weeks after operation the basal metabolic rate was −26 per cent. The patient returned home on a maintenance dose of viosterol and calcium gluconate.

The patient was seen again 4 months after operation, at which time she was in excellent health and had regained the 40 pounds previously lost. The only complaints were soreness of the shins and ankle edema, which appeared only with walking. These phenomena were attributed to the prolonged period of confinement to bed. The basal metabolic rate was −1 per cent, the serum calcium 10.2 mg. per 100 cc., the serum phosphorus 3.1 mg., the phosphatase 1.1 Bodansky units, and the hemoglobin 14.9 gm.

Pathological report: The thyroid tissue when removed weighed 53 gm., was homogeneously pink, and showed a few small nodular areas. Histologic sections revealed closely spaced follicles, some of which were lined with low cuboidal cells and others with tall columnar cells (Fig. 1). The stroma was richly vascularized, and there were occasional collections of lymphoid tissue. The findings were typical of hyperplasia of the thyroid gland with iodine involution.

At the left lower pole of the thyroid gland was a parathyroid gland weighing 2.5 gm. Microscopic examination disclosed closely packed cells in cords, with occasional alveolar formations. The cells were polyhedral and small, and contained finely granular and slightly basophilic cytoplasm with round nuclei rich in chromatin (Fig. 2). Some of the alveolar formations were lined with these cells and contained small amounts of pinkish material. There were numerous eosinophils in the highly vascular stroma. The pathological diagnosis was adenoma of the parathyroid gland.[1]

Cases in the Literature

We were able to find in the literature 5 cases of this combination of hyperthyroidism and hyperparathyroidism. Meyer-Borstel's[2] patient had severe Graves's disease associated with generalized osteitis fibrosa cystica. This patient was seen in 1922, at a period when the association between the bone disease and hyperparathyroidism was not clearly defined. Consequently, when she underwent thyroidectomy a parathyroid tumor was neither searched for nor found. Ballin and Morse[3] cited a case with symptoms of hyperthyroidism in which "a calcified adenomatous goiter" was removed. During the next few years the patient developed bone pains and decalcification, and this time a parathyroid adenoma was found at operation. Ball[4] reported a case with an elevated basal metabolic rate and an increased serum calcium, in which the combined diagnosis was made clinically. At operation a "colloid and fetal adenoma" of the thyroid was found. Search for a parathyroid tumor was fruitless. The serum calcium remained elevated after operation. Hellström's patient[5] had a basal metabolic rate of +50 per cent, a serum calcium of 14 mg. per 100 cc. and generalized osteitis fibrosa cystica. She was not subjected to operation. Noble and Borg[6] reported a case that was confirmed at operation. Cooley's patient[7] probably does not fall into this group, for although the basal metabolic rate was +23 per cent, there was a colloid goiter histologically.

Discussion

Our patient's preoperative course was unusual in several respects, and was the subject of considerable discussion. She had taken a daily dose of thyroid for an extended period of time, but this

medication was stopped two months before entry. It was believed that her symptoms of thyrotoxicosis could not be attributed to this. There was a considerable degree of nausea, vomiting, weakness and anemia. These symptoms can occur in hyperthyroidism, but they are not commonly so severe as in this patient. Another confusing symptom was abdominal distress and tenderness. These problems were of course clarified by the finding of a parathyroid adenoma.

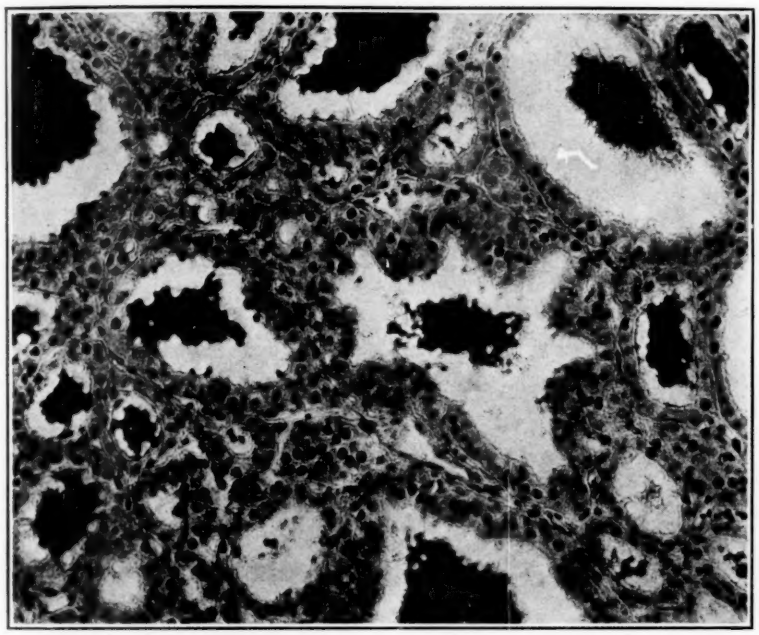

FIGURE 1. *Photograph of Section of Thyroid Gland, Showing Hyperplasia with Iodine Involution (eosin and methylene blue, 200×).*

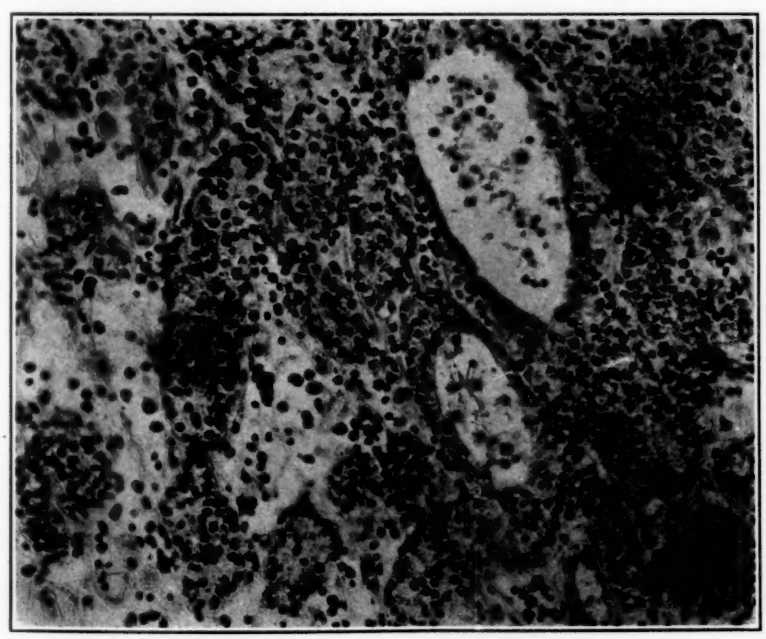

FIGURE 2. *Photograph of Section of Parathyroid Adenoma (eosin and methylene blue, 200×).*

In Table 1 are listed the most frequent symptoms and signs characteristic of hyperfunction of the

thyroid and parathyroid glands, as well as those common to both.[8-11] It is evident from this table that there are striking and confusing clinical similarities. In the presence of thyrotoxicosis there are relatively few factors that lead one to suspect a superimposed hyperparathyroidism. These include osteitis fibrosa cystica, metastatic calcification, marked hypochromic anemia and, of course, increased serum calcium. In the case under discussion, the significant clinical features that could have led to the proper diagnosis were a history of renal stone, abdominal distress, anemia, marked nausea and vomiting, and unusual asthenia.

TABLE 1. *Symptoms and Signs in Hyperfunction of the Thyroid and Parathyroid Glands.*

SYMPTOM OR SIGN	PRESENT IN CASE REPORTED
Common to hyperthyroidism and hyperparathyroidism:	
Mass in neck	+
Weight loss	+
Anorexia	+
Nausea and vomiting	+
Weakness and fatigue	+
Osteoporosis	+
Polyuria and polydipsia	
Increased urine calcium	
Increased serum phosphatase	
Found particularly in hyperthyroidism:	
Nervousness	+
Tremor	+
Tachycardia and palpitation	+
Eye signs	+
Thrill and bruit over gland	+
Perspiration and warmth	+
Pressure symptoms (cough and dyspnea)	+
Diarrhea	+
Oligomenorrhea or amenorrhea	+
Increased basal metabolic rate	+
Good appetite	
Found particularly in hyperparathyroidism:	
Metastatic calcification, especially renal stones	+
Abdominal distress and pain	+
Cold extremities	+
Hypochromic anemia	+
Increased serum calcium and decreased serum phosphorus	+
Osteitis fibrosa cystica, bone pains, bone tumors, fractures and deformities	
Renal insufficiency	
Bradycardia	
Constipation	

One may speculate on a possible common etiologic factor in this syndrome. The obvious link that comes to mind is the pituitary gland. In this patient, however, there was no evidence of pituitary disease.

SUMMARY

A case of simultaneous hyperthyroidism and hyperparathyroidism is presented. Other case reports are reviewed.

The salient factors in diagnosis are summarized.

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COMPLETE SITUS INVERSUS

Report of a Case with Calcareous Aortic Stenosis and Cor Bovinum

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ALTHOUGH congenital cardiac anomalies and defects have frequently been found associated with situs inversus,[1] reports of acquired cardiac lesions are rare. Owen[2] reported a case of mitral stenosis, and King[3] one of syphilitic aortitis, aortic insufficiency, cardiac hypertrophy and myocarditis with a mural thrombus.

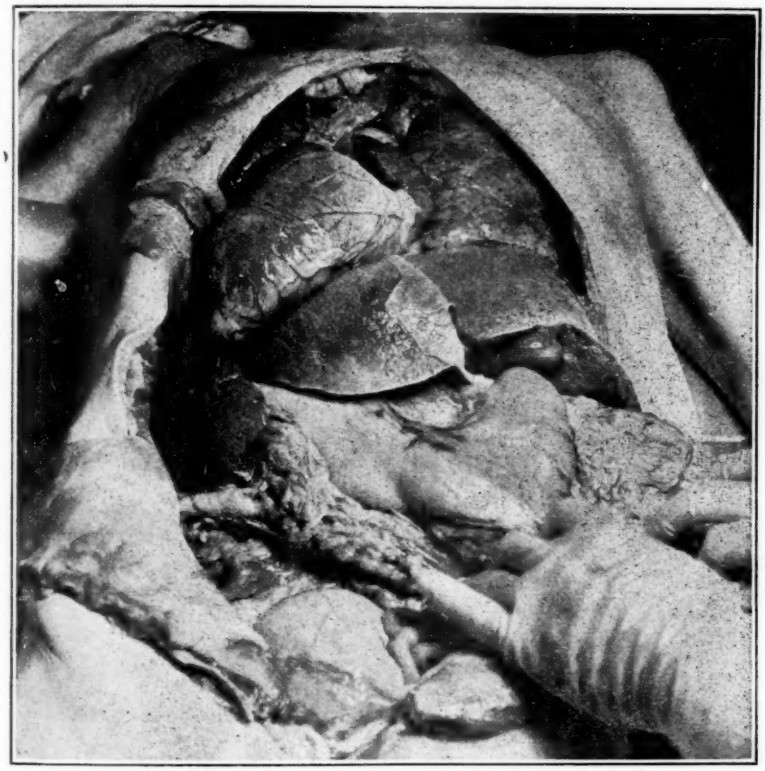

FIGURE 1. *Situs Inversus Totalis.*
Note the greatly hypertrophied heart.

The first case of complete situs inversus with calcareous aortic stenosis, cor bovinum and multiple pulmonary infarcts, is now reported.

CASE REPORT

A 43-year-old Swede entered the United States Marine Hospital on September 15, 1941, because of a cold and productive cough of 3 weeks' duration. He had been treated in this hospital for gonorrheal urethritis in 1938. At that time a diagnosis of dextrocardia with aortic stenosis was made. The patient had no symptoms referable to the heart. There was no history of rheumatic fever. An electrocardiogram was interpreted as showing dextrocardia. There was complete inversion of Lead 1, and transposition of Leads 2 and 3. The heart was compensated, only moderately enlarged, and showed no evidence of myocardial damage. From the age of 15, the patient had worked at laborious occupations, unrestrained. He stated that he had had a serious lung or heart ailment in 1907.

On admission he complained of shortness of breath on exertion, paroxysmal nocturnal dyspnea and swelling of the ankles. He had persistent dull pain in the right chest and a feeling of "rawness" behind the lower sternum.

On physical examination the patient was found to be in moderate distress, in congestive heart failure and cyanotic. There was marked edema of the lower extremities. The pulse was 96, regular, small in volume and equal on both sides. The apex beat was in the right 6th interspace at the anterior axillary line. There was a marked systolic thrill in the 2nd and 3rd intercostal spaces to the left of the sternum. In this area a loud, harsh systolic murmur was heard, which was audible over the entire precordium and in the neck. The aortic second sound

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was replaced by a short, faint diastolic murmur. The liver was palpably enlarged on the left side.

An electrocardiogram showed inversion of the P and QRS waves in Lead 1 and marked right-axis deviation. The T waves were upright in all leads. Comparison of this electrocardiogram with the one made 3 years previously disclosed evidence of left-ventricular strain in the new one. A roentgenogram of the chest gave the maximum heart measurements as 10.8 cm. to the right and 7 cm. to the left; the transverse diameter of the chest was 28.4 cm. A lateral view showed shadows suggestive of aortic calcification. Roentgenograms after a barium meal showed complete transposition of the gastrointestinal tract. The Wassermann and Kahn tests were negative.

The patient responded to treatment for 6 weeks and thereafter went downward. He died December 20.

Autopsy. There was complete situs inversus (Fig. 1). The heart weighed 810 gm. The aortic orifice was stenosed and deformed, and the cusps were fused and massively calcified (Fig. 2). The calcified ring measured 4 mm. in thickness. Microscopic examination showed the calcified cusps to consist of hyalinized scar tissue with more or less cartilaginous metaplasia and calcification. The myocardium was markedly hypertrophied. Microscopic examination revealed scattered areas of interstitial fibrosis and foci of old myocardial scarring. The coronary arteries showed more or less diffuse fibrosis of their walls with occasional foci of atheroma and calcification in the intima. Multiple old and recent infarcts were present in all lobes of both lungs.

FIGURE 2. *Calcareous Lesion of the Aortic Valve.*

SUMMARY

Complete situs inversus associated with calcareous aortic stenosis, cor bovinum and multiple pulmonary infarcts is reported for the first time. The cardiac lesions were compatible with an old rheumatic infection.

I am indebted to Drs. G. A. Abbott and Henry I. Russek for the clinical data used in this report.

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MEDICAL PROGRESS

PATHOLOGY: DISEASES OF BONE

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TO MOST physicians the rarer diseases of bone with their multiple polysyllabic and still more confusing eponymic terminologies constitute the most perplexing field in medicine, a field so esoteric that it is apt to be relegated far back into the realms of the subconscious. This confusion, it must be admitted, is not unwarranted since there is justifiable suspicion that it afflicts the experts to an almost equal, albeit unadmitted, degree. In the last few years enough new observations have been placed on record to help in delineating these various entities to make a summary worth while at the present time.

HAND-SCHÜLLER-CHRISTIAN'S DISEASE, LETTERER-SIWE'S DISEASE AND EOSINOPHILIC GRANULOMA OF BONE

Hand-[1, 2] Schüller-[3, 4] Christian's[5] disease, in its fully developed form as first described by Christian with the triad of multiple defects of cranial bones, exophthalmos and diabetes insipidus, has become a familiar picture, in the textbooks at least, though probably relatively few physicians have actually had a case under their own observation. That other cases lacking one or more features of the triad exist is less well known, and such cases are more likely to escape recognition and report. Yet Bürger,[6] in an assemblage of cases from the literature, found that 22 of 48 cases fell in this category. Also less generally realized is the possibility of other osseous localizations, in the pelvis, ribs, phalanges and even the long tubular bones, of lymph-node and splenic involvement and, still more important, since they are life-endangering, of destructive lesions of the brain itself (Letterer[7]).

For somewhat over a decade, since the comprehensive studies of Rowland,[8] Hand-Schüller-Christian's disease has been classified with the disturbances of lipoid metabolism — Gaucher's disease with its storage of kerasin, Niemann-Pick's disease with phosphatide abnormality and Hand-Schüller-Christian's disease as the corresponding disturbance of cholesterol metabolism. Significant reasons for questioning the correctness of this convenient schematization exist and have recently been re-emphasized (Letterer,[7] Wallgren[9] and Farber[10, 11]).

From the pathological point of view it is evident that Hand-Schüller-Christian's disease is not a simple so-called "storage disease," like Niemann-Pick's or Gaucher's disease. It invariably shows the histological characteristics of a granulomatous process accompanied by significant grades of inflammatory reaction, both leukocytic and fibrotic. Yet cholesterol storage, which can readily be provoked by the feeding of cholesterol to rabbits, does not result in a granulomatous inflammatory reaction. Moreover, the spontaneous familial disease of man characterized by cutaneous xanthelasma, hypercholesteremia and extensive deposits of cholesterol and its esters in tendon sheaths and other tissues — familial xanthomatosis[12, 13] — is not associated with granulomatous reactions and never shows the destructive lesions of bone that characterize Hand-Schüller-Christian's disease. It is also noteworthy that no familial or even racial tendency has ever been noted in the latter, in contrast to the other storage diseases.

Cases of Hand-Schüller-Christian's disease do not ordinarily come to the attention of a physician in the early stages of their development. The bone lesions are usually so slow in their development and so painless that they remain unnoticed for a long period. When, however, the disease has been recognized at a comparatively early period or a fresh lesion is biopsied in a case of longer standing, it has been the usual experience that the granulomatous reaction is present but there is as yet little or no lipoid deposit (Freund and Ripps[14]). Cholesterinization occurs only with progression of the disease and is secondary, not primary (Letterer[7]).

As the significance of cholesterol has diminished in the conception of the pathogenesis of Hand-Schüller-Christian's disease, more attention has been devoted to the antecedent granulomatous reaction and new relations have become apparent. Wallgren,[9] for instance, in an extremely lucid article argues that Letterer-Siwe's[15] disease or aleukemic reticulosis (Letterer[16]), or diffuse reticuloendotheliosis (Siwe[17]), or nonlipoid histiocytosis (Foot and Olcott[18]) is only a variant of the same pathologic process. Typical Letterer-Siwe's dis-

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, Vol. III, 1942* (Springfield, Illinois: Charles C Thomas Company, 1942. $5.00).

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ease rarely occurs beyond two years of age and runs a rapidly and, it is at present believed, inevitably fatal course. It is characterized clinically by fever, skin rash, rapidly progressive anemia and purpura and histologically by marked proliferation of the so-called "reticuloendothelial" (monocytic and clasmatocytic) cells in many parts of the body, particularly the skin, the lymph nodes and the spleen. Occasionally the process simulates neoplasm so that it has been classified with the pseudoleukemias; more often it presents an inflammatory, granulomatous character that suggests infection. Some of these cases show significant amounts of lipoid storage in the proliferating cells. Certain cases, moreover, otherwise typical of Letterer–Siwe's disease, have shown focal destructive lesions of bone, with or without lipoid deposits, quite indistinguishable from Hand–Schüller–Christian's disease (Schultz, Wermbter and Puhl[19] and Wallgren [Case 2][9]). If the series of reported cases are listed in the order of their chronicity, as Wallgren has done, every grade of transition between the two diseases can be seen. In early infancy a malignant course is invariable, and the patient dies before complete development of the lesion, and before time has elapsed sufficient for secondary lipoid degeneration. In later infancy greater chronicity is the rule and some of the features of Hand–Schüller–Christian's disease begin to make their appearance. From the age of two onward the disease is ordinarily chronic, lipoidal stages develop with considerable frequency, and by the age of three or four the typical picture of Hand–Schüller–Christian's disease is the rule.

A third condition, independently described as a new disease entity by Otani and Ehrlich[20] and by Lichtenstein and Jaffe[21] as solitary or eosinophilic granuloma of bone, may well, in the opinion of Farber,[10, 11] be still another variant of the same pathologic entity. The cases described by these two pairs of authors occurred for the most part in children in the later stages of childhood but also in adults, and were characterized by tumorlike destructive swellings of bone, usually single but occasionally multiple. Not infrequently the patients showed low-grade fever and leukocytosis, and occasionally blood smears disclosed significant grades of eosinophilia. Either excision of the lesion or x-ray treatment following biopsy was followed by rapid cure. Histologically the process is a granulomatous inflammatory lesion with marked accumulation of mononuclear phagocytes, often many foreign-body giant cells and variable numbers of eosinophils, sometimes tremendous. In one of Otani and Ehrlich's cases, however, eosinophils were entirely absent. It is interesting to note that the same histological picture was well described in a beautifully illustrated paper by Fraser[22] in 1935 as a variant of Hand–Schüller–Christian's disease.

Farber[11] has collected a group of 10 cases of granulomatous destructive lesions of bone. In this material he was able to find every grade of transition from typical Hand–Schüller–Christian's disease to the eosinophilic granuloma of Otani and Ehrlich and of Lichtenstein and Jaffe. Clinically typical Hand–Schüller–Christian's disease may show in various lesions xanthomatoid pictures with or without eosinophils, and eosinophilic granulomas without lipoid degeneration. My own experience with 5 cases, only 2 of which have yet been published,[23, 24] is entirely in accord with these findings. Among these cases was an example of clinically typical Hand–Schüller–Christian's disease in a child, in which a lymph-node biopsy yielded the typical picture of eosinophilic granuloma without lipoid deposits; also there were 2 cases in adults with solitary lesions of the cranial bones, one with and one without eosinophils, but both showing extensive cholesterol deposits and the characteristic histologic picture of Hand–Schüller–Christian's disease.

One final variation in the picture remains to be mentioned. Farber points out that in certain cases in children the eosinophil proliferation may be so rapid that differentiation is incomplete and eosinophilic myelocytes may dominate the histologic reaction. The possibility of confusion with neoplastic processes of the myeloid series of cells is very great, and beyond question certain of these lesions have been classified as myelomas and myeloblastomas by competent observers.

Strongly suggestive evidence therefore lies at hand that all these various syndromes represent a single disease entity — rapidly fatal in the infantile forms, which have been described as Letterer–Siwe's disease and reticuloendotheliosis; chronic, but still of serious import because of the likelihood of cerebral and hypophyseal involvement, in early childhood (Hand–Schüller–Christian's disease); and comparatively benign in later childhood or in the adult, where the usual picture is that of eosinophilic granuloma. Proof of this identity must of course await the discovery of the etiology. Recent pathological studies point strongly away from a fundamental metabolic disorder and in the direction of a specific infectious agent.

Osteitis Fibrosa Disseminata, Polyostotic Fibrous Dysplasia, Regional Fibrocystic Disease and Albright's Disease

Under the terms listed in the above heading and more than a score of other names, examples have been recorded of a confusing group of skeletal lesions for some of which fairly clear clinical and

pathologic pictures are beginning to emerge. The most extensive skeletal changes are usually found as part of a syndrome that includes changes in the skin and in the function of certain endocrine glands. The syndrome has been most clearly described by Albright and his numerous collaborators,[25, 26] although individual case reports have been found dating back at least to von Recklinghausen. The essential features are as follows: multiple destructive lesions of bone simulating closely the generalized osteitis fibrosa of hyperparathyroidism and renal rickets but showing a distinct tendency to unilateral distribution; pigmented spots in the skin, also often restricted to one side of the body; and precocious puberty in female but not in male patients. An unusual feature of the precocious puberty associated with this syndrome, sharply separating it from other forms such as may occur with adrenal or ovarian tumors, is that there is no loss of fertility. Indeed one patient with this disease, a Peruvian girl, Lena Medina, won world-wide notoriety when she was delivered of a child at the age of five.[27]

It is clear that the bone lesions are not due to abnormal parathyroid activity. Although the blood calcium and phosphatase may be moderately elevated in the active stages of the disease, the phosphorus is never depressed and there is no increased excretion of calcium in the urine. The uninvolved bones fail to show the generalized decalcification characteristic of hyperparathyroidism. Finally, under mistaken diagnosis, the parathyroid glands have several times been explored and on one occasion the removal of two normal glands was followed by unmistakable symptoms of tetany.[28]

As in Hand-Schüller-Christian's disease, however, there is reason to doubt that all cases, or even, in the opinion of Lichtenstein and Jaffe,[29] any considerable proportion of them, present the complete triad of bone lesions, skin pigmentation and precocious puberty. Female patients with typical bone and skin lesions may not give a history of precocious puberty. Characteristic multiple bone lesions of unilateral distribution are found without skin pigmentation or endocrinopathy. Monomelic involvement — the restriction of lesions to the bones of a single extremity — has frequently been observed. Finally, single lesions of bone — so-called "osteitis fibrosa localisata" — are comparatively common which by x-ray and on gross and histologic examination of excised specimens are indistinguishable from individual lesions of the disseminate type.

From the clinical point of view, certain similarities between the localized and disseminate forms are apparent. The lesions usually appear in youth, commonly in later childhood or adolescence. Their development is evidently slow and often associated with little pain. Consequently they may remain undiscovered for long periods of time until a pathologic fracture and consequent x-ray examination call attention to their presence. After a certain period they tend to become quiescent, although it is doubtful if they ever spontaneously heal and disappear. Little evidence exists, however, that the localized disease ever tends to become generalized. Both flat and tubular bones may be involved, and in the latter the epiphysis is almost always spared. Although the metaphysis is most frequently involved, even the midportion of the diaphysis may be the site of a lesion.

From the roentgenologic point of view the lesions closely simulate those of hyperparathyroidism, with the notable exception that the uninvolved bones are completely normal without evidence of generalized decalcification.[27, 30] The process appears primarily destructive and usually expansile, with marked thinning of the cortex and no periosteal reaction unless complicated by fracture. Usually the density of the bone is considerably, though often irregularly, diminished and the picture frequently suggests cyst formation, an impression belied by the pathologic findings, which rarely show cyst formation of more than microscopic dimensions in the midst of solid tissue.

When one of these lesions is explored it is found to consist of fibrous tissue of variable density, which usually feels gritty. Microscopic examination proves this to be due to spicules of poorly formed and often imperfectly calcified membranous bone which, in the opinion of Lichtenstein,[31] is formed by metaplasia from the fibrous tissue. In some cases islands of hyaline cartilage are present.

In the opinion of Lichtenstein and Jaffe[29] this histologic picture is sufficiently distinctive to be regarded as specific, even pathognomonic. If they are correct, another not uncommon condition must be brought into the fold. This is the tumor, or at least tumorlike condition, of the jaws that has been variously reported as ossifying fibroma and fibrous osteoma.[31–34] As Lichtenstein[31] has pointed out, the histologic picture is identical with that of fibrous dysplasia. As in the latter disease the onset is in youth, usually in adolescence, and the outlook is favorable.

The majority of observers are as yet unprepared to accept the opinion of Lichtenstein and Jaffe that the histologic picture is pathognomonic, and point out that osteitis fibrosa is seen in hyperparathyroidism, in renal rickets, in some stages of Paget's disease and perhaps even in certain infectious lesions of bone. Lichtenstein and Jaffe, in contrast, assert that in most cases with a biopsy of adequate dimensions there are sufficient differences in the character of the bone formation and bone destruction as well as in the fibrous tissue substrate to

make distinction readily possible. The wealth of material provided by the clinic of the Hospital for Bone and Joint Diseases is so great, and the authors have evidently studied it with such thoroughness and care, that their opinions deserve the most serious consideration.

In another direction also the specificity of the lesion they have described has been challenged. This is shown by the frequent use of the term "fibrocystic disease,"[35] under which solid and cystic lesions have been indiscriminately grouped. Jaffe and Lichtenstein,[36] again, have given special consideration to cystic disease of the bone. Under the name of "solid unicameral bone cyst" they describe their experience with 19 cases of true bone cyst. These are solitary, fluid-filled lesions of long tubular bones, most often of the humerus and femur. The surrounding cortex is expanded and thinned. The lining is ordinary fibrous tissue. They arise in youth, particularly in adolescence. The process starts in apposition with an epiphyseal line, but if untreated may extend to involve the major portion of the shaft. With growth, normal bone may be laid down between the cyst and the epiphyseal line so that the lesions may appear to migrate toward the center of the shaft.

Whatever the ultimate verdict may be regarding the specificity of fibrous dysplasia and the relation of the localized and disseminate forms, this group of lesions well warrants increased attention from clinician and pathologist alike. The former should be on his guard to pick up the localized form of the disease in any patient with a history of repeated fractures, particularly those of the same bone. He must likewise guard by careful blood-chemical determinations against confusing the generalized disease with hyperparathyroidism and subjecting his patient to a needless cervical operation. For the pathologist the greatest danger in this group of lesions lies in the possibility of confusion with malignant neoplasms, particularly in cases complicated by fracture and atypical reparative processes. The development of sarcoma in such a lesion has yet to be reported. Extreme caution should be observed in the face of scanty and possibly inadequate biopsies, and the precaution of checking with expert radiologic opinion should never be omitted.

In the realm of therapy little new has been offered. Nothing whatever is known that will affect the progress of the disseminate disease. Individual lesions in important bones may be treated by curettage, packing with bone chips or the use of solid bone grafts. Recurrence, however, is not infrequent. Radiation therapy is entirely ineffective.

The etiology of this entire group of lesions remains completely mysterious. Their localized character and the well-marked tendency to unilateral distribution rule out a hormonal basis, except, perhaps, as a contributing factor. A congenital abnormality of bone development, possibly mediated in some way through the nervous system, seems the best solution as yet offered. Bremer[37] has suggested an interesting hypothesis based on analogy with the development of the air sac in the humerus of chickens. This has been shown to be dependent on the action of estrin, and the bone is hollowed out immediately below the epiphyseal line by an osteoclastic osteitis fibrosa very similar to the lesion of hyperparathyroidism. The development of lesions during adolescence and their association in certain cases with precocious puberty would fit such a theory. Although of great interest, it is manifest that any such hormonal influence could explain only a part of the picture.

Osteoid Osteoma

Under this title Jaffe[38, 39] and Lichtenstein[40] have described what appears to be a new disease entity probably clinically misinterpreted heretofore as sclerosing, nonsuppurative osteomyelitis or cortical bone abscess. The lesion proper consists of a rather small spherical nodule of vascular mesenchymal tissue closely packed with osteoblasts, which quickly lay down intercellular osteoid tissue that is slow to calcify. Eventually, however, calcification and even hypercalcification beyond the density of normal cortical bone occur. Equally characteristic of the process is the stimulation of reactive proliferation in the surrounding bone, so that the small primary focus is more or less encapsulated by a comparatively large mass of newly formed and very dense cortical bone. The lesion has been seen in nearly all the bones of the extremities and also in the vertebras, but has not as yet been observed in the skull, pelvis or ribs. It develops in youth, commonly between the ages of ten and twenty-five, and appears to be more frequent in males than in females. Almost invariably, the principal symptom is pain, which is extremely persistent but generally not of great intensity, since several months commonly elapse before the patient comes under surgical observation. Local examination usually reveals tenderness and slight swelling. There are no systemic evidences of infection, such as fever and leukocytosis, and there is seldom any convincing history of trauma.

The roentgenographic picture constitutes the most valuable single diagnostic guide but is frequently misinterpreted. In the early stages of the disease the osteoid osteoma proper is indicated by a round or oval focus, 0.5 to 1.0 cm. in diameter, of relative radiolucency. This is surrounded by a perifocal reaction of newly formed and very dense bone, which may be limited to a relatively

narrow ring or may spread for several centimeters about the lesion. Later in its evolution, when the osteoid osteoma tends to become calcified, it no longer appears as an area of uniform rarefaction but begins to show focal and later complete opacity. This is the stage at which it is very apt to be misinterpreted as a sequestrum. To bring out the details of the lesion overexposed plates are frequently necessary.

Treatment in all the cases yet reported has consisted in excision of the osteoid focus and of the overlying reactive bone. This has been followed by immediate relief of pain, and no recurrences are on record.

The etiology remains mysterious. Infection seems to be ruled out by the absence of systemic reaction, by the complete absence of histologic evidence of inflammation in the lesion itself and by the negative results of all bacteriologic investigations. The pathologic picture in no way resembles that of aseptic necrosis of bone, and there is rarely a convincing history of trauma. Jaffe[38, 39] strongly supports a neoplastic origin. Against this must be cited the limited growth capacity of the primary osteoid focus, which regardless of duration rarely exceeds 1.5 cm. in diameter.

Caisson Disease of Bone

Aseptic necrosis of bone of infarctlike character without demonstrable cause for vascular occlusion has long been recognized as the anatomic basis of Legg–Perthes's, Osgood–Schlatter's, Koehler's and Kienböck's diseases. Kahlstrom, Burton and Phemister[41] have recently reported 4 cases of extensive aseptic necrosis, involving numerous bones, in victims of caisson disease. The lesions are limited to the long tubular bones of the extremities. When the lesions were situated in the epiphyses and bordered on joints, collapse of weight-bearing portions usually occurred, overlying articular cartilage broke down, osteocartilaginous loose bodies often appeared, and extensive arthritis deformans developed. When the necrotic bone focus was not in approximation with a joint surface, collapse did not occur and attempts at organization were apparent, but only in the smaller foci was this ever complete. In the larger areas the necrotic focus persisted indefinitely (up to thirty-five years in one case) with only a narrow shell of densely calcified reactive bone at its periphery. The pathogenesis is discussed by these authors, and two alternative theories are contrasted. The first is intravascular air embolism. Against this was the absence in one autopsied case of any infarcts of internal organs despite multiple foci in the bones. Secondly, the attempt to reproduce the picture in animals by air embolism was unsuccessful. The alternative concept is the extravascular liberation of gas bubbles in such numbers that circulation is arrested by extravascular tension. In favor of this theory is the restriction of lesions to the tubular bones, which contain fatty rather than hematopoietic marrow. It has been shown that fat tissue absorbs four to five times as much nitrogen under conditions of increased pressure as do other kinds of tissue. Therefore far more gas is available for release, and its sudden liberation within a nonexpansible bony shell may adequately explain the development of the lesion.

It should be pointed out, however, that indistinguishable multiple lesions of bone have been observed by Chandler[42] and more recently by Kahlstrom, Burton and Phemister[43] in patients who have never been exposed to high atmospheric pressures. The general pathogenesis of aseptic necrosis of bone therefore remains as heretofore an unsolved problem.

Melorheostosis

This formidable name is derived from two Greek words meaning "limb" and "I flow." It refers to the extraordinary appearance of affected bones on x-ray examination. This was originally described by Léri and Joanny[44] as *coulée de bougie*, because of its resemblance to the incrustations of molten wax along the side of a candle. Franklin and Matheson[45] have reported another case and reviewed the literature, which now includes 39 cases.

The affected bones are markedly thickened by irregular cortical overgrowths which project chiefly outward, although some encroachment on the marrow cavity may also occur. Usually multiple bones of a single extremity are involved and there is no greater frequency in the upper than in the lower limbs. Bilateral involvement has been observed in 5 cases, whereas the case of Franklin and Matheson showed almost perfect unilateral distribution, including the parietal and mandibular bones, the innominate bone and two ribs, as well as the tubular bones of the extremities, a more frequent site. Nine vertebras likewise showed changes limited to the right side of the neural arch, but a single vertebra, the fifth lumbar, showed bilateral involvement. Histologic examination showed distortion and compression of the bone pattern with increased osseous density and a proportionate decrease in the number and size of the Haversian canals. There was evident predominance of bone formation over destruction, and although rare osteoblasts were identified, no osteoclasts were seen. The marrow was usually fibrous.

The symptoms of this unusual disease are vague and may be little more than the discomfort of the greatly increased weight of an affected limb. On examination, asymmetry of the face or limbs is usually apparent and nodular bony thickening may

be felt. The x-ray appearance of the *coulée de bougie* is pathognomonic.

Albers-Schönberg Disease, Marble Bones or Osteopetrosis

In this disease, which usually makes itself apparent in early childhood, the bones are of unusual density as judged by x-ray examination but of abnormal fragility from the clinical point of view, since they are prone to sustain repeated fractures from mild trauma. The underlying defect appears to be an inability to resorb bone, so that when new bone is laid down during growth the old bone is not removed. This may lead to pinching of nerves at their points of exit from the skull, and van Creveld and Heybroek[46] report blindness due to optic atrophy as the first symptom in a child. When the normal bone markings are not completely obliterated it is not unusual to see in x-ray films of the extremities transverse lines of increased density, which parallel the epiphyseal line. These are similar to the lines that can be produced experimentally by the intermittent feeding of phosphorus. Van Creveld and Heybroek made the interesting observation that these lines were laid down seasonally, the maximal density occurring in the autumn. With the failure of bone resorption, medullary cavities may fail to develop normally, leading to a myelophthisic anemia. The spleen and liver may be enlarged by compensatory myelopoiesis, and primitive cells of both the erythroid and myeloid series may be found in the peripheral blood. In certain cases the hematologic abnormalities completely dominate the clinical picture.

Metabolic studies in the hands of Kramer, Yuska and Steiner[47] showed normal levels in the blood for calcium, magnesium, phosphorus and phosphatase. Chemical examination of the bone showed hypermineralization and an increase in the carbonate content. Further studies are, however, desirable since their case was complicated by moderately severe rickets.

The etiology of the disease is completely mysterious. The condition is evidently congenital and has been noted at birth. Drukker[48] in a survey of 121 cases found a familial incidence in 40 per cent.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28511

PRESENTATION OF CASE

First admission. A sixty-five-year-old physician was admitted because of a sense of oppression in the chest and "wheezing" at night.

Fourteen years prior to admission he was accidentally found to have a blood pressure of 200 systolic, 130 diastolic, and auricular premature beats. Accordingly he gave up smoking and took potassium sulfocyanate, 1½ gr. three times a day every other month. Two years later the blood pressure was 190 systolic, 100 diastolic.

Eleven years previously, after working particularly hard, he noted a slight amount of dizziness, occasional episodes of ringing in the ears and subcutaneous hemorrhage of the left arm. Physical examination revealed subconjunctival hemorrhage of the left eye. The heart was enlarged, the apex being 10 cm. to the left of the midsternal line in the fifth intercostal space. The heart sounds were of good quality, and a harsh systolic murmur was audible at the apex and in the aortic area; no diastolic murmurs were heard. The pulse was irregular, owing to the presence of many premature beats, and the blood pressure was found to be 195 systolic, 115 diastolic. Fluoroscopic examination revealed a slight amount of cardiac enlargement and a marked tortuosity of the aorta, with a prominent knob. The patient was advised to limit his activities further, and to continue the potassium sulfocyanate medication as previously taken.

Four months before entry he noted a sense of dizziness and mild headache; at times he felt sluggish. He occasionally had to rest because of a feeling of mild chest oppression and an occasionally associated feeling of breathlessness. At that time he was taking aminophyllin, 3 gr. three times a day. Physical examination was unchanged except that the blood pressure was 230 systolic, 130 diastolic. The fluoroscopic examination was repeated and revealed a large left ventricle and a dense aorta; the lung shadows were normal. An electrocardiogram showed a normal rhythm of 75, moderate left-axis deviation and a slight diphasic T_1.

Six weeks prior to entering the hospital he developed a mild "nasal" infection, which persisted to the time of admission without variation in degree, accompanied by occasional slight elevation of temperature. One week before entry the feeling of chest oppression became more severe, exertional dyspnea developed and the patient felt "wheezy" at night.

Physical examination revealed a well-developed and well-nourished man in mild respiratory distress suffering with a mild upper respiratory infection. Examination of the heart showed the maximum apical impulse to be 11 cm. to the left of the midsternal line in the fifth intercostal space. The heart sounds were regular and of fair quality. At the base of the heart over the aortic area a moderately loud, slightly harsh systolic murmur was audible. To the left of the lower sternum a very soft blowing diastolic murmur was heard. At the apex of the heart a moderately loud slightly coarse systolic murmur and a diastolic third heart sound were heard, and these carried toward the lung base. Rales were audible at both lung bases posteriorly. The abdomen was flat and soft, and the lower edge of the liver, which was tender, was felt two fingerbreadths below the costal margin. No other abdominal masses were felt. There was no ankle edema.

The blood pressure was 200 systolic, 110 diastolic. The temperature was 99°F., the pulse 78, and the respirations 20.

The examination of the blood revealed a hemoglobin of 12.4 gm. and a white-cell count of 5100 with 82 per cent polymorphonuclears, 12 per cent lymphocytes and 6 per cent monocytes. The blood Hinton test was negative. The nonprotein nitrogen was 28 mg. per 100 cc. The urine had a specific gravity of 1.010, was acid in reaction and gave a + test for albumin; the sediment contained a rare hyalin cast, 4 red cells and 1 white cell per high-power field. An electrocardiogram showed a normal sinus rhythm, with a rate of 60. T_1 and T_2 were inverted and sagging; T_4 was rather sharply inverted; and there was a moderate amount of left-axis deviation. An x-ray film of the chest demonstrated that the heart lay horizontally in the chest and that there was considerable enlargement of the left ventricle. The curve of the ventricle was prominent and the apex was blunted. The aorta was tortuous and prominent in the region of the knob and showed some calcification in its walls. There was also a slight bulge of aorta near the root. The lung fields were clear.

Three days after admission the patient noticed a slight amount of blood on his pajamas. This was attributed to congestion of a hyperplastic prostate. After ten days the patient improved with bed rest and digitalis. His apparent upper-respiratory-tract infection subsided, and he was able to

get about satisfactorily without great discomfort. He left the hospital in the late afternoon.

Second admission (12 hours later). The patient returned to the hospital because of midepigastric discomfort, nausea and vomiting which had developed a few hours after a rather heavy supper. There was no substernal or back pain. The patient was obviously uncomfortable and was sweating. The examination of the heart revealed good heart sounds, a regular rhythm and murmurs as previously noted. Good vessel pulsations were felt in the legs. The lungs were normal. There was tenderness and some spasm over the entire abdomen, most marked on the right side, opposite and above the umbilicus. The tenderness was less striking in the right lower quadrant. The liver did not appear to be enlarged. There was questionable tenderness over the gall bladder. The peristaltic sounds at times seemed diminished. The rectal examination was negative except for slight enlargement of the prostate.

The blood pressure was unchanged, 200 systolic, 110 diastolic. The temperature was 99°F., the pulse 50, and the respirations 25.

The white-cell count was 20,000. The urine examination was negative except that the sediment contained 3 white cells per high-power field. An electrocardiogram was similar to the previous ones.

The patient was operated on two hours after admission.

Differential Diagnosis

Dr. T. D. Jones: The initial complaint suggests that the patient had coronary disease and a decrease in his cardiac reserve. One soon learns that he had persistent hypertension, the pressure remaining elevated at every determination over a period of fourteen years. There is little evidence that potassium sulfocyanate had any ameliorating effect. Dizziness, headaches, and ringing in the ears may be taken as a part of his hypertensive syndrome. Broken conjunctival blood vessels also occur in hypertensive patients.

Although the stature of the patient is not described, it is assumed that he was of average size. As would be expected, the heart was distinctly enlarged, and there was left-axis deviation by electrocardiogram. Initial fluoroscopy verified the clinical impression of hypertensive heart disease in a patient with definite arteriosclerosis, at least of the thoracic aorta. The murmurs described are not especially unusual in a patient with hypertension and arteriosclerosis. In a patient with these findings, a sense of oppression in the chest warrants a diagnosis of angina pectoris — and a consideration of the presence of coronary sclerosis. This was obviously considered to exist, since he was given aminophyllin. There is no definite indication that it was beneficial. Breathlessness was probably associated with the decrease in cardiac reserve.

For a few months prior to admission and especially for the preceding six weeks, there was an apparent increase in symptoms. On admission there was evidence of mild congestive heart failure, along with an increase in the feeling of chest oppression. This failure may have been precipitated by the recent mild respiratory infection that was thought to have persisted to the time of admission. The exact nature of the respiratory infection is impossible to determine in retrospect.

Failure was indicated by respiratory distress, slight enlargement of the liver, rales in the lung bases, and concomitant urinary changes. There was an obvious increase in the severity of the heart disease over previous examinations as indicated by the heart size. This is not surprising in view of the persistent hypertension and the story of slowly diminishing cardiac reserve. It is rather surprising that there was no evidence of actual renal disease after so many years of hypertension.

The murmurs are distinctly in keeping with the hypertensive and arteriosclerotic process and need not raise the question of rheumatic valvular disease. There was no evidence of aortic stenosis; syphilitic aortic disease seems unlikely in view of his age, the negative Hinton test, the absence of a syphilitic history and the prolonged period of symptomatology. A diastolic murmur resulting from syphilitic aortitis usually develops prior to symptoms, rather than after a long period of decreased cardiac reserve resulting from this condition.

The electrocardiograph was not too helpful. The changes raise the question of a previous slow occlusion of the coronary vessels. This suggestion must remain as a possibility despite no history of an acute coronary episode. The sharply inverted T_4 is suggestive, and certainly corroborates the impression of extensive heart disease.

The x-ray findings reiterate the question of the presence of sclerotic changes, at least in the ascending aorta. In view of the terminal episode the question naturally arises whether or not the arteriosclerotic process was more progressive than was apparent.

The question of finding blood on the patient's pajamas is confusing and does not help clarify the underlying process. As reported it is impossible to connect it directly with the patient's illness.

The second and final admission, twelve hours after hospital discharge, seems unquestionably a problem of an acute abdominal condition. In view of the previous history and findings, one would naturally expect the episode to be related to the hypertensive and arteriosclerotic syndrome, espe-

cially the latter. The acute symptoms began three or four hours prior to readmission to the hospital, and evidently were not too severe, otherwise immediate surgical intervention would have ensued. It would be helpful to know what happened to the blood pressure during this period, as it is distinctly lowered as the result of appreciable hemorrhage, of dissection of an arterial aneurysm and of acute coronary closure. So far as I am aware, it may or may not be lowered in mesenteric thrombosis. However, on admission the pressure was very near its previous high level.

Apparently there was no chest pain to suggest acute coronary closure, nor was shock so severe as one might expect in extensive hemorrhage or extensive aneurysmal dissection. Also against the latter is any indication of direction of dissection, usually suggested by the radiation of pain. It hence seems more likely that thrombosis or infarction of the mesenteric vessels comes nearer satisfying the general features presented by the abdominal emergency. Mesenteric thrombosis therefore is my preoperative diagnosis. This would not be too unusual in a person with long-standing hypertensive heart disease and coronary sclerosis, with some question of previous coronary closure. It seems likely that arteriosclerosis was the fundamental basis for the difficulty.

Dr. Paul D. White: I saw this man in 1931 on two occasions because of his hypertension. He was apparently symptom-free at the time. He did not have an aortic diastolic murmur but only an aortic systolic murmur, which, because of his hypertension, I was inclined to think was not due to valvular disease. Dr. Edward Bland later raised the question whether the aortic systolic and diastolic murmurs were of rheumatic origin. He simply raised that question, but it is unlikely that at this patient's age there had occurred sufficient additional rheumatic disease to produce an aortic diastolic murmur.

A Physician: In the presence of extensive calcareous valvular disease, could there be some degree of regurgitation?

Dr. White: I think that is more of a possibility here than rheumatic involvement, if there is any valvular disease at all.

A Physician: Is not the story different from that of aortic stenosis of significant degree? Would you not expect him to have died sooner?

Dr. White: No. A good many patients do have acute failure,—left ventricular failure,—but not until ten or more years after the accidental finding of a murmur undoubtedly due to aortic stenosis. They can even live some years after the heart failure starts, despite a high degree of aortic stenosis.

Dr. Jones: Can such a systemic pressure be sustained with aortic stenosis?

Dr. White: Yes, it can be done. I have seen a number of such cases.

Dr. Ernest M. Daland: If you could have seen this patient yourself it would have been obvious that he had an acute abdominal condition with his maximum tenderness and spasm in the right upper quadrant, just above the umbilicus. There was questionable tenderness over the gall bladder, but he gave no history of previous gall-bladder disease or ulcer. Although he had a good deal of rigidity in the right upper quadrant, he did not have a board-like belly and a perforated ulcer was ruled out on that basis. He did not have enough localized tenderness over the gall bladder to make a diagnosis of acute cholecystitis. The possibility of appendicitis was considered. It seemed as if his acute abdominal condition must have had some relation to the previous illness, and so the diagnosis of mesenteric thrombosis was thought most likely. Under general anesthesia the abdomen was opened through a rather high midline incision. We found the appendix and gall bladder free of disease, and the liver was normal. The chief finding was a large retroperitoneal hematoma. This was below the level of the pancreas, at the root of the mesentery of the small bowel. It looked somewhat like an acute hemorrhagic pancreatitis except that there was no fat necrosis and we were able to palpate the pancreas separately from the mass. The mass was 8 to 10 cm. in diameter. The intestines showed good color, and no mesenteric thrombosis was found. We could not feel any aneurysm, and no further exploration was made. The postoperative diagnosis was retroperitoneal hemorrhage. The patient made a good recovery from operation. At the end of the operation his systolic blood pressure was down to about 100, but during the next few hours it returned to 200 and he felt quite well during the remainder of the day. He asked what the operative findings were and discussed the diagnosis quite intelligently. About four o'clock the next morning, about twenty-four hours after the operation, he suddenly went into collapse and was dead in a minute or two.

Dr. Tracy B. Mallory: At operation, a large retroperitoneal hematoma was found, source not determined. Does anyone care to speculate any further on the diagnostic possibilities?

Dr. Jones: I presume he had an aneurysm that ruptured into a closed space. That changes the diagnosis from probable mesenteric thrombosis to a dissecting type of lesion.

Dr. White: Do you think it was necessarily a dissecting aneurysm? Could it have been hem-

orrhage from a saccular arteriosclerotic aneurysm of the abdominal aorta?

Clinical Diagnosis

Mesenteric thrombosis.

Dr. Jones's Diagnoses

Hypertensive heart disease.
Coronary sclerosis.
Mesenteric thrombosis.

Anatomical Diagnoses

Acute hemorrhagic pancreatitis with fat necrosis.
Retroperitoneal hematoma.
Slight hemoperitoneum.
Cardiac hypertrophy.
Arteriosclerosis: marked, aortic; moderate, pulmonary and coronary.
Nephritis, vascular, chronic.
Pulmonary edema.
Operative wound: exploratory laparotomy.

Pathological Discussion

Dr. Mallory: We had considerable difficulty at the time of autopsy in determining the cause of the hemorrhage. The great bulk of the hematoma lay in the mesentery, which had been dissected into two leaves by the blood. Tracing this back we eventually tracked it down to the posterior surface of the head of the pancreas, where we found numerous areas of fat necrosis. At this point there was characteristic acute hemorrhagic pancreatitis, so-called "pancreatitic apoplexy." A peculiar feature was that the blood instead of dissecting profusely through the pancreas had dissected largely into the root of the mesentery. The pancreatitis was limited to the posterior portion of the head of the pancreas. The body and tail were normal. It would not have been possible to recognize it at the time of operation because it was not until we approached the organs from behind that we found it ourselves.

The other findings were a markedly hypertrophied heart, weighing 550 gm. The coronary arteries were large and capacious with some arteriosclerotic plaques but no occlusion at any point, and the myocardium showed no areas of infarction. The aortic valve was entirely negative. There was no calcification, no stenosis or no regurgitation. The kidneys showed the characteristic nephrosclerosis to be expected in long-standing hypertension.

Dr. White: There are two things I should like to emphasize with respect to this case. First, there can be long-standing aortic systolic murmurs and even aortic diastolic murmurs without valvular disease. Second, the electrocardiogram of a large hypertensive heart can closely resemble that of coronary heart disease.

Dr. Mallory: The ascending aorta was markedly sclerotic. So far as thrombosis is concerned there was no gross calcification but a little dilatation, and the aortic ring itself was of normal measurement.

Dr. Daland: Do you not think it surprising that no more was found in the pancreas at the end of thirty hours?

Dr. Mallory: It is very unusual.

CASE 28512

Presentation of Case

First admission. This forty-four-year-old man was admitted because of a persistent cough.

One year prior to admission the patient developed a cough, which at times was productive of a slight amount of gray-white sputum. When he coughed he occasionally had substernal pain, but this was never severe. Four months before entry the cough increased and a greater amount of sputum was raised; this was thick and yellow but did not have an odor and never contained blood. At that time both ankles became swollen and stiff. His physician said that the edema was not of a "pitting type" and that the urine was normal. Despite the medication provided the cough was unimproved. The leg edema gradually increased to the knees, the ankle stiffness became more marked, and the knees became stiff, swollen, painful and slightly red. He also developed exertional dyspnea. During the entire period the cough became progressively worse.

One week before admission an electrocardiogram was said to have been normal. A chest roentgenogram disclosed some cloudiness in the lower left lung, but no diagnosis was made. A single sputum was negative for acid-fast bacilli. He was treated with "wheat-germ oil" injections, and two days later the joint pain and most of the leg swelling disappeared. During the week prior to admission he raised one fourth of a cup of sputum each day, which was very thick and had developed a foul odor. During the six months prior to entry he had lost 27 pounds.

The patient's mother died of "carcinoma of the throat," and his father died of heart trouble. The past history was noncontributory.

Physical examination revealed a prematurely gray man who was hoarse and who coughed frequently making him uncomfortable because of the associated chest pain. The heart was percussed 10 cm. to the left of the midsternal line. The heart sounds were of good quality, and no murmurs

were heard. There was decreased expansion of the left chest, with dullness over the upper left chest anteriorly and increased breath and voice sounds in this area. Scattered fine rales were audible at the left apex, and a friction rub was heard in the left midaxillary line. Examination of the abdomen was negative. There was swelling with some pitting edema of both lower legs. The ankles were slightly swollen but were not warm, red or tender. There was marked clubbing of the fingers and toes.

The blood pressure was 120 systolic, 70 diastolic. The temperature was 101°F., the pulse 95, and the respirations 30. The temperature and pulse continued to rise each evening.

Examination of the blood revealed a hemoglobin of 9.1 gm., a white-cell count of 20,800 with 88 per cent polymorphonuclears. The urine repeatedly was acid in reaction, had a specific gravity of 1.028 and gave a + test for albumin; the sediment contained 7 red cells and occasional white cells and epithelial cells per high-power field. The blood Hinton test was negative. The blood protein was 5.9 gm. per 100 cc., with 2.8 gm. albumin and 3.1 gm. globulin, making the albumin-globulin ratio 0.9. The sputum examination was negative for acid-fast bacilli on two occasions. A chest roentgenogram showed diffuse hazy density of the entire left lung field, and within this area there was a fairly sharply defined rounded mass lying posteriorly against the ribs and extending from the fourth to the eighth rib. There are multiple areas of rarefaction within this mass, and there were similar areas of rarefaction anterior to it in the right upper lobe. The mediastinum was displaced to the left. The left side of the diaphragm was high, and the left costophrenic angle was obliterated. There was no evidence of disease in the right lung, and the visible ribs and vertebras showed no evidence of metastases.

On the third day after admission the patient was bronchoscoped. There was no widening deviation or fixation of the carina. At a point in the left bronchial tree about 5 or 6 cm. below the carina the left main bronchus became narrowed and presented an irregular granular appearance on the lateral as well as the medial aspect. The left upper lobe orifice was not seen. Foul bloody secretion was aspirated, and several biopsy specimens were taken, which were reported as showing acute and chronic inflammation. On the ninth hospital day a left upper lobe abscess was drained posteriorly by resecting segments of the fifth, sixth and seventh ribs. The abscess was described as immense. It contained a moderate amount of gangrenous lung and small amounts of pus. It was traversed by several septums. Sulfanilamide powder was implanted locally. A pleural biopsy was reported as showing acute and chronic pleuritis. The culture of the pus demonstrated a few alpha-hemolytic streptococci and a moderate growth of nonhemolytic streptococci. After operation, the patient improved and the temperature and pulse returned to normal. He was discharged on the thirty-third day after admission.

Second admission (one month later). The patient was readmitted for study of the persistent ankle edema. After discharge there was little drainage from the chest. One week before entry the cough was slightly increased but little sputum was raised. Since the previous admission he had suffered with a great deal of exertional dyspnea but at no time was he orthopneic.

On examination the patient was plethoric and puffy faced, and coughed frequently. The neck veins were not distended. The trachea was slightly deviated to the left. The heart was percussed 8 cm. to the left of the midclavicular line. The sounds were regular and of good quality. There seemed to be a split second sound audible at the apex. No murmurs were audible. There was a large cavity in the left posterior chest, from which a small amount of foul pus drained. Bronchial whistling was audible over this area. The left chest was dull on percussion. The abdomen was held tensely; however, no fluid was found and no masses were definitely felt. There were dilated veins in the lower abdominal wall. Clubbing of the fingers and toes was again noted. There was no evidence of phlebitis.

The urine and blood examinations were similar to those noted during the previous admission. The nonprotein nitrogen was 14 mg. per 100 cc., the chloride 98.8 milliequiv. per liter, and the protein 5.5 gm. per 100 cc., with an albumin of 3.0 gm. and a globulin of 2.5 gm., giving an albumin-globulin ratio of 1.2. An electrocardiogram showed a normal sinus rhythm with a rate of 90. The PR interval was 0.16 second; T_1 was flat, and T_2, T_3 and T_4 were upright. The Congo-red test showed 100 per cent retention of the dye in the serum after one hour.

He was treated with a course of sulfathiazole, totaling 12 gm. in four days, and was discharged unimproved nine days after admission.

Third admission (two months later). The patient was readmitted because of painful swelling and stiffness of the knees and ankles, which developed soon after leaving the hospital. The pain was dull and occurred intermittently each day, being worse in the morning, but at no time was it severe. The joints were not red or warm. During the three weeks prior to admission the pa-

tient had gained 10 pounds. The chronic cough had persisted, and occasionally there was blood streaking of the sputum. While at home he took sulfathiazole, which was later changed to sulfadiazine because of nausea, "dizziness" and the development of a rash on the face. He had nocturia, one or two times, and occasional urgency. He had not had any fever or rise of blood pressure.

Physical examination was similar to that already noted except that there was swelling of the ankles without redness, tenderness or pitting edema. There was no pain or limitation of leg-joint motion.

Examination of the blood revealed a hemoglobin of 10.7 gm. and a white-cell count of 20,300 with 64 per cent polymorphonuclears. In the smear the red cells appeared normal, and the platelets were slightly increased. The nonprotein nitrogen was 30 mg., and the protein 7.2 gm. per 100 cc. No acid-fast organisms were found in the sputum. The urine had a specific gravity of 1.010 and gave a + test for albumin; the sediment contained 15 white cells, a rare red cell and 3 epithelial cells per high-power field; the pH was alkaline on three occasions and acid on two. A phenolsulfonephthalein test showed 17, 8, 12 and 15 per cent excretion of the dye in a quarter, a half, one and two hours respectively. A chest film showed little change in appearance since the last entry. The greater portion of the left upper lobe was honeycombed in appearance, showing numerous small cavities. The large abscess cavity was no longer definitely visible. The fluid in the left base had cleared. There was some inspiratory shift to the left, and the mediastinum was displaced to this side. The right lung field remained clear.

The patient was treated with 4 gm. of sulfadiazine and discharged unimproved on the third day after admission.

Fourth admission (two months later). The patient was readmitted for left pneumonectomy. Since discharge he had gained weight but continued to have cough and hemoptysis. He became dyspneic on climbing a flight of stairs. Ankle edema had not been severe.

Physical examination was similar to that of previous admissions.

The temperature was 98.6°F., the pulse 80, and the respirations 22.

The hemoglobin was 9.8 gm., and the white-cell count 16,900 with 65 per cent polymorphonuclears. In the smear the red cells were fairly normal, but the platelets were slightly increased. The urine was acid in reaction, had a specific gravity of 1.012 and gave a + test for albumin; the sediment contained 2 hyaline casts, occasional finely granular casts, 15 red cells, 15 white cells and 2 epithelial cells per high-power field. A phenolsulfonephthalein test showed 23, 20, 20 and 10 per cent excretion of the dye in a quarter, a half, one and two hours respectively. The nonprotein nitrogen was 18 mg. per 100 cc., the protein 5.9 gm., and the sulfadiazine level 5.9 mg.

A 7-gm. course of sulfadiazine was administered in the five days after admission.

An operation was performed on the eighth day after admission.

Differential Diagnosis

Dr. John W. Cass: This history could be compatible with a number of things; it raises the question of tuberculosis, abscess and some type of bronchial obstruction with slowly increasing infection. The suggestion of swollen joints and the edema cannot be evaluated as yet with the mere facts of the history. They do suggest pulmonary osteoarthropathy with some evidence of cardiac or renal failure. There is definite evidence of pulmonary disease in the x-ray films of the chest, and little evidence of congestive failure.

I do not know why "wheat-germ oil" was given. I certainly should like to know if anyone cares to offer the information.

Dr. Joseph C. Aub: We have tried it out in cancer with equivocal results; it contains a large quantity of vitamin E. I had nothing to do with its use, however, in this case.

Dr. Cass: The pulmonary process became contaminated with mouth organisms, and undoubtedly there was abscess formation, which raises the question whether it was abscess from the beginning. I should doubt this from the sequence of events; I think that the primary disease process simply became contaminated with these organisms and that abscess formation occurred.

Extreme loss of weight is compatible with lung abscess or other suppurative lung conditions, as well as tumor, malignant or benign, with or without infection.

Apparently the patient was having real pain, which is against tuberculosis and more compatible with abscess or tumor. Was more than one sputum specimen examined for tubercle bacilli?

Dr. Tracy B. Mallory: At least three sputum examinations were negative for tubercle bacilli.

Dr. Cass: I think we can feel fairly confident that we are not dealing with tuberculosis. Although clubbing can occur very quickly under certain conditions, its sudden development is rare; it points against tuberculosis but is perfectly compatible with tumor plus infection or suppurative infection alone.

The physical signs I interpret as those of solid mass, with peripheral atelectasis and pleural in-

volvement as the explanations why he was having so much pain.

I should say that the edema was not associated with the heart but with kidney involvement secondary to the septic process in the chest. The urine showed evidence of kidney irritation. The serum protein was a trifle low, the albumin definitely low; the ratio was inverted so that although the total protein was not greatly below normal I think it is still compatible with sufficient kidney damage to cause some degree of edema.

May we see the x-ray films?

DR. LAURENCE ROBBINS: The entire process is on the left. This is the large cavity that is spoken of; the other areas of density in the large cavity are seen better in the lateral view and lie anterior to the large cavity. The right lung field is clear.

DR. CASS: The x-ray findings strengthen our belief that we are not dealing with tuberculosis or pure infection of any type. There is a distinct description of a mass, and it is well known that any type of malignant mass in the chest can have cavities within it or behind the obstruction that the mass causes. From the bronchoscopist's report we get confirmation of bronchial obstruction with suppurative disease in back of the obstruction. The only infectious state that would produce this would be tuberculosis with involvement of the bronchial wall as well as the parenchyma. But we have several negative biopsies, which are quite important in ruling out tuberculosis but not tumor. As a matter of fact the appearance of bronchial tuberculosis is so characteristic that the bronchoscopist would scarcely need to take a biopsy. We have not ruled out malignant tumor, however, on the basis of the negative bronchoscopic examination and biopsy.

It was apparently obvious that the suppurative situation could not be adequately drained by postural or bronchoscopic drainage, and external drainage had to be instituted.

This apparently changed the course very little, and it was necessary to readmit the patient after a month, primarily for study of his edema. His heart seemed essentially normal, and I believe his dyspnea was chiefly mechanical, perhaps due to displacement of the mediastinum. He then had a bronchial fistula, as would be expected, and no essential change in the primary disease. I still believe that the edema was secondary to the pulmonary disease. I do not attach any particular significance to the abdominal veins, in spite of the fact that they might indicate liver damage. The nonprotein nitrogen was within normal limits — a bit low. The total protein was low, and the albumin-globulin ratio essentially normal. Even though this is true, the lowered total protein was getting to the point where one would expect edema. So far as the Congo-red test goes, this rules out amyloid disease. It is rather strange how seldom one makes a clinical diagnosis of amyloid disease in suppurative diseases of the chest, but I am not sure how much significance can be placed on a perfectly normal Congo-red test.

At the third admission the patient apparently had improved a bit, unless the gain in weight was due to edema. But I believe it was probably a true gain in weight. The persistent pain I think is adequately explained as pulmonary osteoarthropathy, and he still had edema. It is apparent that the drainage was not adequately taking care of the pulmonary situation. He had reached the point where as much as possible had been gained by the drainage, and an attempt was made to correct the primary situation.

He was admitted for the fourth time for operation, pneumonectomy. It is definite that there were bronchial obstruction and pulmonary suppuration with multiple cavities, and the question is whether we can explain this process on the basis of infection alone, of tumor or of some other form of bronchial obstruction plus suppurative disease behind the obstruction. It is possible, I suppose, to have a lung abscess beginning with such a type of history as this with a gradual development of foul sputum. I cannot visualize, however, a bronchial obstruction occurring secondary to abscess, and we know from bronchoscopy that obstruction was present. The only infection that would fit the picture is tuberculosis, but we have definitely ruled out tuberculosis by the multiple sputum examinations and by the biopsy. If this man had been fortunate enough to have had tuberculosis this series of procedures would have been proper, — namely, the drainage of a large cavity and, later, a pneumonectomy, — but I believe he was not so fortunate as to have this disease. So we are left with tumor with abscess formation behind the obstruction. The tumor could be benign, but we do not have the proper history for a benign tumor. There was not the long story of cough and intermittent episodes of infection so commonly associated with this type of obstruction. A tumor was not seen on bronchoscopic examination, and although it is more or less guesswork from this point on, I should say that we are dealing with a malignant type of obstruction, in spite of the negative biopsies. The course was certainly relatively benign for the usual bronchiogenic carcinoma. We have a right to mention primary sarcoma — a very rare tumor and one that may very well fail to yield a positive biopsy. However, I think we should pick the commoner type of disease, which

is bronchiogenic carcinoma, in spite of the history of repeatedly negative biopsies.

Dr. William B. Breed: I cannot refrain from suggesting lymphoma as a strong possibility for no good reason except bitter experience in the past.

Dr. John W. Strieder: As Dr. Cass said, certainly the sequence of steps was correct and one has the right to suspect underlying disease — I certainly agree with Dr. Cass that carcinoma is the best bet.

Clinical Diagnoses

Carcinoma of lung, with necrosis and abscess formation.
Sulfonamide nephrosis.

Dr. Cass's Diagnoses

Carcinoma of the lung (bronchiogenic).
Bronchial obstruction, with pulmonary suppuration.
Nephrosis (septic).
Pulmonary osteoarthropathy.

Anatomical Diagnoses

Epidermoid carcinoma of lung.
Abscess of lung.

Pathological Discussion

Dr. Mallory: Two interesting features invite discussion — the primary pulmonary process and the edema and the signs in the urine. Since we did not get permission for an autopsy, I cannot say anything about the kidneys, and I suppose it is profitless to speculate about them. In regard to the lungs, total pneumonectomy was done with a preoperative diagnosis of chronic lung abscess, but with the consideration that there might possibly be carcinoma behind it. Inasmuch as they were not able to prove the presence of carcinoma, it was believed that the patient should be given the benefit of the doubt and the chance of cure by pneumonectomy.

At the time of operation it became evident as the operation progressed that the surgeon was forced to cut through neoplastic tissue close to the hilus of the lung. He had to continue at that stage with the pneumonectomy, which was successfully carried out. The operative wound healed well, with complete apparent relief of the pulmonary symptoms, but the patient slowly developed further evidence of renal insufficiency and died three weeks after operation.

The lung showed a large abscess cavity near the base of the upper lobe. The walls of this cavity consisted primarily of fibrous tissue and showed no neoplasm. Above this major abscess cavity, however, was a spherical tumor mass, in the midst of which was a second abscess cavity, and the walls of this upper cavity were neoplastic. The major abscess that was seen in the x-ray plates was, I believe, the lower benign one. That is what was drained at the first operation, and no tumor was encountered at that time. Nor was any found there when we finally had the entire lung in our possession. The bronchus leading to this area was occluded by external pressure from extension to the hilus of the tumor, which originated near the apex of the lung. The tumor was a poorly differentiated epidermoid carcinoma.

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HOSPITALS AND COMPULSORY HOSPITAL INSURANCE

"Every governmental energy must be concentrated on winning the war. Reforms or making America over cannot but dislocate the war effort." This statement by Ex-President Hoover in his twelve points of vital interest to the Home Front is so axiomatic that it should delay additional social-security legislation until the war has been won. Regardless of its virtues or defects, legislation that will profoundly affect the postwar American way of life should be postponed for consideration with other peacetime readjustments. However, since bills of this type have already been submitted to Congress and since silence might be taken for assent or approval, discussion appears to be necessary.

Such a bill, "To amend and extend the provisions of the Social Security Act; to establish a federal social-insurance system; to extend the coverage of federal old-age and survivors' insurance; to provide insurance benefits for workers permanently and totally disabled; to establish a federal system of unemployment compensation and temporary disability benefits and a federal system of unemployment offices; to establish a federal system of hospitalization benefits; to amend the Internal Revenue Code; and for other purposes," has been introduced by Representative Thomas H. Eliot, of Massachusetts. Without consideration or comment on the other parts of the bill, the proposal "to establish a federal system of hospitalization benefits," or, in other words, "compulsory hospital insurance," as it is commonly called, deserves critical comment.

At the present time in the United States there is a widespread and rapidly growing system of voluntary hospital insurance known as the Blue Cross Plan. The basic philosophy underlying such voluntary hospital insurance is radically different from that of compulsory hospital insurance, in spite of their aiming at the same objective.

Voluntary insurance, as its name implies, connotes a voluntary act on the part of the insured, as the result of consideration and decision. It requires thinking. Thus it exemplifies the essence of democracy. By thinking, choice and action the subscriber becomes a better citizen, and by the development of his will and initiative the community is benefited and improved. It is a slow process, but sure.

Compulsory insurance, likewise, is self-descriptive for it means that all persons falling within its provisions shall, willy-nilly, comply with its regulations. There is no opportunity for choice or decision. Essentially it is taxation under another name. It is regimentation held to be justifiable by the claim that it is for the benefit of the insured, that it spreads the burden and that it forces the improvident to provide. Its proponents claim that it will achieve in one year what voluntary insurance would require many years to accomplish

and that it would eliminate charity and so increase the self-respect of former recipients. They compare by analogy the anticipated benefits of compulsory hospital insurance to the good accomplished by the Workmen's Compensation acts, forgetting that in the latter case no voluntary plan was available.

Voluntary hospital insurance has been available for ten years. New and not understood, growth during the early years was slow. It has rapidly expanded during the last five years, and now over ten million people are insured under this plan. It is spreading rapidly. Reciprocity between plans is accepted in principle and practice. In collaboration with state and local medical societies, plans for the coverage of medical fees for hospital care are being developed, and in some states are already in operation. Since it operates within state boundaries, it is adaptable to local conditions. Since it is a nonprofit corporation, it is flexible and can adjust to new conditions without resort to legislation. Since it is subject to regulation by state commissions of insurance and welfare, its subscribers are protected from exploitation. Its cost of operation has been uniformly low.

There is no opposition on the part of the American Hospital Association or of most hospital administrators to the provision of better hospitals in rural areas, to the extension of hospital care for certain public-assistance categories, such as the aged, and even to the consideration of compulsory hospital insurance. But they believe that the resulting plan should be the product of collaboration and co-operation by the Social Security Board, hospital representatives, physicians and representatives of the charitable, labor and welfare organizations of the community and that this collaboration should take place at a time when adequate and contemplative consideration can be given to a problem so vitally affecting American life. The American Hospital Association is actively furthering the extension and liberalization of Blue Cross plans, an endeavor that can go on during the emergency without hampering the war effort, since the methods and machinery are already in operation.

Specific defects in the Eliot bill can be noted as follows:

> The proposed federalization scraps the present relation provided by the Social Security Act between the states and the federal government.
>
> The United States is too large and too varied to be adequately legislated for on a matter so vitally influenced by local conditions. States can give better adjustment and control, according to local needs.
>
> The bill requires the setting up of a new bureau for administration and operation at a time when the manpower of the Nation is already overextended, and with the certainty of added cost.
>
> Nothing in the bill remedies the lack of medical care and hospital facilities in rural areas. In fact, the bill expressly prohibits the use of money for this purpose.
>
> The bill does not adequately separate administration and payments for hospitalization and disability benefits. The experiences of European plans point to the necessity of this separation.
>
> The bill as drawn gives no consideration to the necessity of preserving voluntary plans. The present hospital system is based on the co-operation of voluntary and governmental hospitals, which supplement each other in caring for all classes of the community. If compulsory insurance is instituted, certainly a similar co-operation should be provided for with voluntary insurance. Otherwise it will probably mean the gradual destruction of philanthropy, for local interest will be difficult to sustain if the federal government assumes leadership and responsibility. Local morale suffers under remote control, and there would be no incentive for experimentation in different localities to meet varying conditions.
>
> There is no consideration of medical-care fees, a program that is now going forward under the leadership of the voluntary plans.

The problem boils down, finally, to an evaluation of the moral values inherent in voluntary plans contrasted with the expected material values of compulsory plans. It is essentially individualism versus regimentation. Further consideration of such social readjustments should not be undertaken during the stress of war conditions, but should be put off for consideration after the war is won. Probably a satisfactory compromise between the two extremes can then be obtained.

DIPHTHERIA CARRIERS

THE care of the diphtheria carrier has been a perplexing problem for the last fifty years. So many different measures have been heralded as effective and have later proved to be valueless that one is wary of anything new that is brought for-

ward. It has long been known that the hazard of the tonsillar carrier is usually eliminated by tonsillectomy. Furthermore, the removal of a small ball of cellophane or a piece of rubber sponge from a child's nose has promptly brought about a series of negative release cultures. However, when tonsils have been removed and the question of a foreign body in the nose has been eliminated, the experienced physician has learned that other measures aimed at the destruction of the diphtheria organism not only have proved to be futile but have made matters worse by injuring the mucous membrane.

A valuable contribution to the carrier problem has been made by Boissard and Fry* in England. From an elaborate and painstaking study of 388 cases of diphtheria, these authors have found that the presence of substantial numbers of hemolytic streptococci in the nose was frequently responsible for the persistence of positive diphtheria cultures and that, by elimination of the streptococcal element with local applications of sulfanilamide, the diphtherial element promptly disappeared. No drug of the sulfanilamide group has been shown to have a direct influence on *Corynebacterium diphtheriae*, either in vivo or in vitro; therefore, these drugs have no effect on the course of diphtheria. The administration of antitoxin still remains the first principle in the treatment of the disease, but it is of no value in the treatment of the healthy carrier. Indeed, the value of antitoxin in treatment of the disease does not depend on any direct action on the diphtheria organism but on the neutralization of the circulating toxin; this permits the natural protective forces of the body to attack the localized infection effectively. The internal administration of sulfanilamide, as well as its local application, has been tried on carriers, but with unsatisfactory results. These English authors, however, have proved that the drug is effective in nasal carriers in whom *C. diphtheriae* is associated with substantial numbers of hemolytic streptococci.

The treatment consists in insufflating sulfanilamide powder into the nose twice a day for a week. During the following week, cultures are taken every other day. If all these are negative, the patient is released; otherwise, the process is resumed for another week. These authors obtained abrupt and permanent elimination of the diphtheria-carrier state in 24 of 26 nasal carriers after the first week's treatment. In 8 cases of tonsillar carriers, the insufflation of sulfanilamide in the nose and its direct application to the tonsils proved ineffective.

The scholarly attitude exhibited in the report of this experiment offers convincing evidence that a significant step, with well-defined limitations, has been made in the elimination of the diphtheria carrier.

*Boissard, J. M., and Fry, R. M. Chronic nasal diphtheria carriers: cure with sulphanilamide. *Lancet* 1:610-614, 1942.

MEDICAL EPONYM

Sippy Treatment

The first account by Dr. Bertram W. Sippy (1866–1924), professor of medicine in the Rush Medical College, of his method of treating peptic ulcer appeared in the third volume (pages 342–353) of *A Handbook of Practical Treatment* (Philadelphia and London, 1917), edited by John H. Musser and A. O. J. Kelly. He writes:

> . . . . Undoubtedly, hyperchlorhydria is unfavorable to the healing of ulcer. . . . The indication in medicinal treatment should be to reduce the corrosive action of the gastric juice, to diminish the mechanical irritation caused by food, pressure, peristalsis, and active movements of the body, to provide adequate nourishment and to treat the symptoms and complicating conditions as they arise. . . . During the first five days no food or drink is given by mouth. . . . At the end of five or six days one may begin to feed half an ounce each of milk and cream every hour from early morning until eight or nine o'clock at night. . . . Midway between each feeding a powder consisting of 10 grains each of calcined magnesia and sodium bicarbonate may be given alternately with a powder of 10 grains each of bismuth subnitrate and sodium bicarbonate. . . .

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SOCIETY HEADQUARTERS

Owing to the shortage of fuel oil, the Boston Medical Library will be closed on Saturdays, commencing December 19 and continuing until further notice. This will

necessitate the closing of the headquarters of the Society and the office of the *Journal* during the corresponding period. In an emergency, the officers of the Society and the managing editor and associate editors of the *Journal* can be located through their offices or homes.

COMMITTEE ON MATERNAL WELFARE

Analysis of Causes of Maternal Death in Massachusetts during 1941

Toxemia and Eclampsia

Twenty-seven maternal deaths during 1941 were attributed to toxemia and eclampsia. The term "eclampsia" in this classification applies to pregnant patients who had actual convulsions. Among these patients, there were 7 with convulsions and 1 with a severe toxemia but no convulsions who were delivered by cesarean section. This is noteworthy, since it is generally accepted that undelivered eclamptic patients who are not in labor have the best chance of recovery if they are treated with extreme conservatism. Twenty-five years ago, convulsive patients not in labor were treated by *accouchement forcé*. Because of the extremely high mortality of the patients so treated, manual dilatation of the cervix and subsequent operative delivery gradually came to be frowned on, so that today it is gratifying to note that not one case of eclampsia in this series was so treated. After *accouchement forcé* had been discarded, the belief that emptying the uterus removed the cause of disease and thus enhanced the patient's chance of recovery led to a very general adoption of cesarean section as the treatment of this complication. That any operative interference was ill advised was first brought out by the Stroganoff method of treating eclampsia. Some modification of this conservative method has been proved to be the accepted method of procedure. In some clinics, nothing is done other than sedation of the patient and the intravenous administration of magnesium sulfate—there is no operative intervention. To this conservative treatment, other clinics have added artificial rupture of the membranes for the purpose of inducing labor, and statistics in the clinics where such cases are so handled are so much better than those where cesarean section is done that the latter has been practically abandoned. This being so, it is interesting to analyze the fatal cases of eclampsia delivered by cesarean section.

The first patient was a primipara who died forty hours following a classical cesarean section. The prenatal care was sketchy and probably not adequate. She was about seven months pregnant when three convulsions occurred. A 2½-pound baby, who lived for a short while, was delivered. This case quite probably would not have been fatal had the convulsions been treated symptomatically by intravenous magnesium sulfate, sedatives and, possibly, induction of labor by artificial rupture of the membranes. It is fair to say that the method of treatment in this case would not have obtained in most clinics.

The second case was that of a patient seven and a half months pregnant who had been showing pre-eclamptic symptoms—a systolic blood pressure of 140 and a large trace of albumin in the urine. Because of this she was sent to the hospital for delivery by cesarean section on the following day. During the night the blood pressure rose to 180, and while she was being prepared for operation, a convulsion occurred. A living premature baby was delivered by cesarean section, but the patient did not regain consciousness. In view of the present knowledge of obstetrics, conservatism might have averted this fatality. The prenatal care in this case was adequate if not the most intelligent.

The third case was that of a primipara who had had a previous nephrectomy. She was followed intelligently during the prenatal period but when about thirty-four weeks pregnant developed marked edema and a systolic blood pressure of 180. In spite of hospitalization, the toxemia did not abate; cesarean section was done and a living child delivered. Nine days postpartum convulsions appeared, and death followed within twenty-four hours. Unfortunately there was no autopsy. The late post-partum eclampsia probably means that the remaining kidney suffered permanent damage, which resulted in total kidney failure. In all honesty, it seems unlikely that the cesarean section was much more than a contributing influence in this fatality.

The fourth patient was a primipara approximately at term whose prenatal care was neither intelligent nor adequate. Convulsions occurred before labor, and a cesarean was done because the cervix was not "favorable." Death occurred thirty-six hours after delivery.

The fifth patient had had a previous cesarean section in 1933. She was adequately taken care of prenatally, and at the seventh month was hospitalized because of a systolic blood pressure of 170. Hospital treatment did not relieve the toxemia, and when the patient was about seven and a half months pregnant an extraperitoneal cesarean section of the Waters type was done, but death occurred a few hours after delivery. This patient

may have had myocardial failure, which occurs occasionally in patients with severe toxemia. As she was not in labor and as the membranes had not been ruptured, it is difficult to understand why the Waters operation was performed. In this case, convulsions did not occur.

The sixth case was that of a primipara who, at approximately seven and a half months, developed toxemia associated with vomiting of blood, jaundice and a systolic blood pressure of 220. Hospitalization was recommended and accepted. The morning of the entry the patient's blood pressure came down to 164 systolic, 100 diastolic, but rose to 230 systolic, 120 diastolic in the afternoon. A classical cesarean was done under spinal anesthesia, and a living baby weighing 2 pounds, 12 ounces, was delivered; death occurred shortly after delivery. One can only wonder whether conservatism would have averted this catastrophe.

The seventh patient was a multipara who had had six previous pregnancies and was said to have had toxemia in her second and fourth pregnancies. In the seventh month of her last pregnancy the systolic blood pressure rose to between 160 and 200, and she was hospitalized. Convulsions occurred and increased in severity, and consequently a cesarean section was performed. Death occurred thirty-two hours later. The history of this case is not adequate and, of course, a cesarean section in a multipara with eclampsia has no justification.

The history of the eighth and final case is not adequate. Eclampsia existed in a patient on whom a cesarean section was performed; presumably an autopsy was done because the diagnosis of focal necrosis of the liver was made.

(*To be concluded*)

DEATHS

FRENCH — Ralph W. French, M.D., of Fall River, died December 7. He was in his sixtieth year.

Born in Fall River, he attended Harvard University and received his degree cum laude from Harvard Medical School in 1910. After serving his internship at the Massachusetts General Hospital he joined the staff of the Truesdale Hospital.

He was a fellow of the Massachusetts Medical Society and the American Medical Association. He was also a member of the American College of Surgeons, the New England Surgical Society and the Fall River Medical Society.

His sister and an aunt survive him.

KENEALY — Joseph H. Kenealy, M.D., of Natick, died in Chicago, December 2. He was in his sixty-fifth year.

Born in Natick, he received his degree from Harvard Medical School in 1900. He practiced in Boston for several years before taking up residence in Chicago. He was a former member of the Massachusetts Medical Society.

His widow and a daughter survive him.

WAR ACTIVITIES

CIVILIAN DEFENSE

Red Cross Mobile Canteens

The following directive was recently forwarded to all regional directors, regional medical heads and deputy regional medical heads of the Massachusetts Committee on Public Safety.

* * *

1. Some misunderstandings may have developed due to the fact that medical mobile canteens were not mentioned in *Medical Handbook No. 2* of the Massachusetts Committee on Public Safety. The Red Cross has agreed to provide a determined number of such mobile canteens properly equipped and with trained personnel that shall become the local units of the Medical Division in supplying civilian war aid, although maintaining their identity and insignia. Should the situation be of such magnitude to require additional assistance, the Medical Division will then call, through appropriate channels, on the Massachusetts Women's Defense Corps, held in reserve for such purposes, or on whatever other supplementary resources are available. Local plans at variance with these terms shall, on request of any party, be submitted to the executive director of the Massachusetts Committee on Public Safety for amendment or approval by him after consultation with the Red Cross.

2. The "determined number" of mobile canteens varies not merely with the population but with local needs. In some communities one mobile canteen may be sufficient to service two or three towns combining two or three medical first-aid posts; in others the ratio may run as high as one mobile canteen for each medical first-aid post. In the larger cities where several first-aid posts are included in one medical depot, a ratio of 40 per cent of the number of auxiliary ambulances involved is the accepted quota.

3. Auxiliary ambulances accompanying the physicians and their medical units should be the first to arrive at the scene of the incident, but mobile canteens with hot liquids for the treatment of shock should not be far behind.

4. Heretofore, in most localities, mobile canteens have not participated in "practice alerts." With the adoption of the audible signal for "yellow" or "green" lights, it will now be necessary for these units to mobilize.

It is suggested that plans be developed between chief medical officers and Red Cross liaisons whereby mobile canteens shall proceed to the prearranged spot where they plan to obtain their supply of hot liquids and so forth, and stand by for instructions from the chief medical officer whether to prepare and load such hot liquids, to proceed to the medical depot, medical first-aid post or incident or to dismiss. Where canteen equipment is stored at the medical depot this procedure will be unnecessary in "practice alerts," *but in any case, mobile-canteen vehicles must mobilize on the preliminary audible signal.* Chief medical officers must remember they are standing by and not forget to dismiss them.

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Director, Medical Division
Joseph R. Hamlen, American Red Cross Liaison
First Service Command
18 Tremont Street
Boston

MISCELLANY

TUBERCULOSIS IN COLLEGE STUDENTS

A second five-year review of tuberculosis in college students, marking the close of a decade of service by the Tuberculosis Committee of the American Student Health Association, reveals heartening progress, along with the stern challenge that tuberculosis still clings tenaciously to first place among causes of death in those of college age. Three hundred and four colleges and universities reported tuberculosis programs for 1940–41 as against one hundred and four in 1936–37, but this represents a bare 36 per cent of American institutions of higher education. Ancient and erroneous notions about tuberculosis still persist in the minds of many college administrators, which unhappily limit the adequacy of their college health services. The truth must be carried to these people ceaselessly and convincingly, if tuberculosis is to be dislodged from the American college campus. The following abstract of a recent article on the subject (Lyght, C. E. Tuberculosis in college students: a second five-year review. *Am. Rev. Tuberc.* **46**:227–237, 1942) is of interest.

The Tuberculosis Committee of the American Student Health Association was formed in 1931 following the first National Conference on College Hygiene at Syracuse University. At that time six institutions of higher education were known to have begun tuberculosis programs — the state universities of Minnesota, Michigan and Pennsylvania, Western Reserve University, Vassar and Yale. At the close of the first five years of the Committee's work, fifty colleges reported programs. Now, at the end of the second five years, three hundred and four institutions so report. This number represents every section of the country, and includes endowed colleges and universities, state colleges, institutes, teachers' colleges and universities, and civic colleges and universities. State universities made the best showing; the small, privately endowed colleges the least satisfactory.

In 1936–37 there were ninety-one colleges using the tuberculin test on 56,224 students; in 1940–41, two hundred and fifty-five colleges were doing so, and the number of students taking the test had increased to 149,744. The percentage of institutions using the Mantoux method dropped in this period from 88 to 82. Recent experiments in some localities with patch testing, along with some schools using the Pirquet method because the state supplies only that type of testing material, account for the drop.

The number of colleges using routine chest films without prior tuberculin testing increased from 12 per cent in 1936–37 to 16 per cent in 1940–41. A few colleges and universities have adopted miniature-film mass surveys.

There has been an encouraging increase in the number of colleges examining nonstudent personnel. In 1936–37, thirty colleges required the examination of food handlers, and twenty-nine the examination of the faculty and administrative employees, while in 1940–41 there were one hundred and eight colleges reporting the examination of food handlers and ninety-two the examination of the faculty and administrative personnel.

The annual reports of the Tuberculosis Committee have disclosed a startling difference in the amount of tuberculosis in students discovered in colleges with case-finding facilities and in schools with no program of case finding. In the second five-year period, 1936–41, the colleges in the latter category reported the discovery of 184 new cases of tuberculosis among a student enrollment of 668,895, a rate of 27.5 per 100,000. The colleges with case-finding facilities reported the discovery of 3523 new cases in a student enrollment of 1,850,755, a rate of 190.5 per 100,000, during the same period.

Roughly, this confers a ratio of 7:1 in favor of the progressive colleges dedicated to the proposition that tuberculosis must be tracked down to its lair, found early and treated promptly, if it is to be defeated ultimately in the individual and in the Nation. These figures imply that thousands of cases of tuberculosis, many of them infectious, are being harbored and ignored among American college students through utter failure of most colleges to comprehend that a threat to health truly exists and that a major social and economic problem clamors for action.

Letters from college administrators attempting to justify the nonexistence of case-finding programs in their respective institutions indicate the prevalence of such ancient ideas as, that only when "consumption" arrives is tuberculosis present, that early tuberculosis can be ruled out by a physician's cursory certification or by stethoscopic search, or by stratified social selection. The survival of these fallacies among educated people represents our failure to carry the truth ceaselessly and convincingly to every person whose information, no matter how complete in most directions, remains barren with respect to tuberculosis.

The war, which in its train brings conditions of overcrowding and overwork, the disruption of public and private medical services, the curtailment of budgets and the restriction of personnel, gives opportunity also for the increase of tuberculosis unless special efforts are made to guard against this menace. Army, Navy, industry, public health — all must fight together and against tuberculosis, but it is of the very essence and function of education that colleges and universities lead the battle.

It is suggested that just as counties were once accredited for eliminating tuberculosis from their dairy herds, even as today they are being accredited in Minnesota for driving death rates and infection rates to low levels, colleges and universities might be accredited by the American Student Health and the National Tuberculosis associations, once they have inaugurated and maintained acceptably a modern program against student tuberculosis. Laggard colleges might thus be tempted to make the necessary adjustments so that they could be listed on the Roll of Honor of progressive, public-spirited institutions.

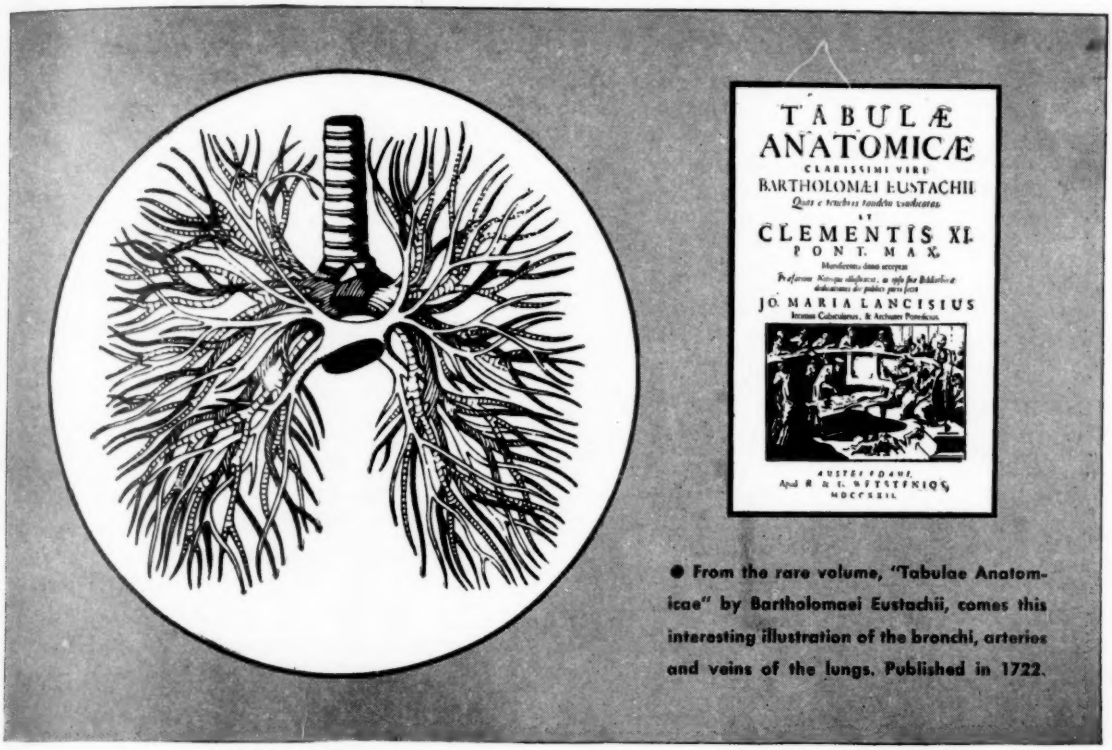
The war must go on. The war must be won, and we must win it, both from our external foes and from such borers-from-within as tuberculosis. — Reprinted from *Tuberculosis Abstracts* (December, 1942).

BOOK REVIEW

War Department. Technical Manual TM 8–240. Roentgenographic technicians. 8°, paper, 223 pp., with 109 illustrations. Washington, D. C.: Government Printing Office, 1941. 35 cents.

This manual contains about 70 pages of descriptive material and a series of reproductions to show the position of the patient and the resulting radiograph. The descriptive material includes several chapters on the physics of magnetism and electricity, as well as chapters on the operation of an x-ray machine. The material as presented is in general correct, although there are a number of minor errors that might easily have been corrected had the manuscript been submitted to a physicist before printing.

(Notices on page x)



● From the rare volume, "Tabulae Anatomicae" by Bartholomaei Eustachii, comes this interesting illustration of the bronchi, arteries and veins of the lungs. Published in 1722.

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NOTICES

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Sunday, December 20

Monday, December 21

•12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

Tuesday, December 22

•12:15–1:15 p.m. Clinicoroentgenologic conference. Peter Bent Brigham Hospital amphitheater.

Wednesday, December 23

•12:00 m. Clinicopathological conference. Children's Hospital.

Saturday, December 26

•10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

•Open to the medical profession.

February 13. American Board of Obstetrics and Gynecology. Page 690, issue of October 29.

May 18, 19. Massachusetts Medical Society. Springfield.

District Societies

BRISTOL SOUTH
May 6. New Bedford.

ESSEX NORTH
January 6.
May 5.

ESSEX SOUTH
January 6. Danvers State Hospital.
February 3. Lynn Hospital.
March 3. Essex Sanatorium.
April 7. Addison Gilbert Hospital, Gloucester.
May 5. Salem Country Club.

FRANKLIN
January 12.
March 9.
May 11. Annual meeting.

All meetings are held at 11:00 a.m. at the Franklin County Hospital, Greenfield.

HAMPSHIRE
January 6.
March 3.
May 5.

MIDDLESEX EAST
January 27.
March 17.
May 5.

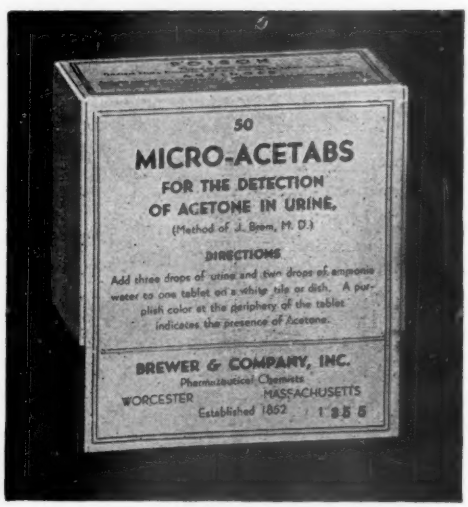
All meetings are held at the Bear Hill Golf Club, Stoneham, at 12:15 p.m., except that of May 5, which will be held at 6:30 p.m.

MIDDLESEX NORTH
January 27.
April 28.
July 28.

PLYMOUTH
January 21. Brockton Hospital.
February 18. Jordan Hospital, Plymouth.
March 18. Goddard Hospital.
April 15. Bridgewater State Farm.
May 20. Lakeville.

WORCESTER
January 13. St. Vincent Hospital, Worcester.
February 10. Worcester State Hospital, Worcester.
March 10. Memorial Hospital, Worcester.
April 14. Hahnemann Hospital, Worcester.
May 12. Annual meeting.

WORCESTER NORTH
January 27.
April 28.
July 28.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*A Simple Micromethod for the Detection of Acetone in Urine. Brem, J., *New Eng. J. Med.*, 224:462, 1941.

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